Modelling the potential role of control strategies on Ebola virus disease dynamics

by

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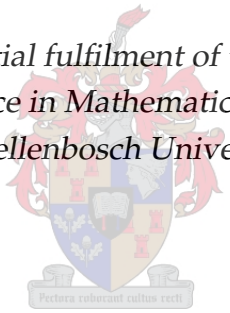
Thesis presented in partial fulfilment of the requirements for the degree of Master of Science in Mathematics in the Faculty of Science at Stellenbosch University



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Declaration

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Abstract

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Thesis: MSc. (Mathematical Biology)

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The most deadly Ebola disease epidemic ever was still ongoing as of June 2015 in West Africa. It started in Guinea, where the first cases were recorded in March 2014. Control strategies, aiming at stopping the transmission chain of Ebola disease were publicised through national and international media and were successful in Liberia. Using two different approaches, the dynamics of Ebola disease is described in this thesis. First, a six compartments mathematical model is formulated to investigate the role of media campaigns on Ebola transmission. The model includes tweets or messages sent by individuals with different disease status through the media. The media campaigns reproduction number is computed and used to investigate the stability of the disease free steady state. The presence of a backward bifurcation as well as a forward bifurcation are shown together with the existence and local stability of the endemic equilibrium. We concluded through numerical simulations, that messages sent through media have a time limited beneficial effect on the reduction of Ebola cases and media campaigns must be spaced out in order to be more efficacious. Second, we use a seven compartments model to describe the evolution of the disease in the population when educational campaigns, active case-finding and pharmaceutical interventions are implemented as controls against the disease. We prove the existence of an optimal control set and analyse the necessary and sufficient conditions, optimality and transversality conditions. Using data from

affected countries, we conclude using numerical analysis that containing an Ebola outbreak needs early and long term implementation of the joint control strategies.

Opsomming

Modellering van die potensiële rol van beheerstrategieë in die Ebolavirus-siektedinamika

("Modelling the potential role of control strategies on Ebola virus disease dynamics ")

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In Junie 2015 was die dodelikste Ebola-epidemie ooit steeds voortslepend in Wes-Afrika. Dit het in Guinee uitgebreek, waar die eerste gevalle in Maart 2014 opgeteken is. Beheerstrategieë daarop gemik om die oordragsketting van Ebola te stop is deur die nasionale en internasionale media gepubliseer en was suksesvol in Liberië. In hierdie tesis word die dinamika van Ebola aan die hand van twee verskillende benaderings beskryf. Eerstens is 'n sesvak- wiskundige model geformuleer om die rol van mediaveldtogte in Ebola-oordrag te ondersoek. Die model sluit twiets of boodskappe gestuur deur individue met wisselende siektestatus deur die media in. Die mediaveldtogweergawenommer is bereken en gebruik om die stabiliteit van die siektevry - ewewigstoestand te bespreek. Die teenwoordigheid van 'n terugwaartse bifurkasie asook 'n voorwaartse bifurkasie is getoon, tesame met die voorkoms en plaaslike stabiliteit van die endemie-ewewig. Ons gevolgtrekking deur middel van numeriese simulasies is dat boodskappe wat deur die media gestuur is 'n tydsbeperkte voordelige uitwerking op die vermindering van Ebola-gevalle het en dat mediaveldtogte gespasieer moet word om meer doeltreffend te wees. Tweedens is 'n sewevak-model gebruik om die evolusie van die siekte onder die bevolking te beskryf as opvoedkundige veldtogte, aktiewe gevalopsporing en farmaseutiese intervensies as beheermaatreëls teen die siekte geïmple-

menteer word. Die studie bewys die bestaan van 'n optimale beheerstel en ontleed die nodige en doeltreffende toestande, optimaliteit en transversaliteitsvoorwaardes. Met behulp van data van lande wat deur die siekte geraak is, is die bevinding ná numeriese analise dat vroegtydige en langtermyn-implementering van die gesamentlike beheerstrategieë nodig is om die uitbreek van Ebola te beheer.

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Dedications

To my lovely daughter Diolvie

Publications

The following publications which are attached at the end of the list of references are the expected publications that would arise from the thesis.

1. Modelling the potential role of media campaigns on Ebola transmission dynamics. Publication to be submitted.
2. An optimal control for Ebola virus disease. Submitted to the Journal of Biological Systems. Publication in review.

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Chapter 1

Introduction

1.1 Ebola: the virus and the disease

Ebola is the name of a small river in the North West of the Democratic Republic of Congo (DRC) where the Ebola virus was first identified in humans in 1976 [13]. Ebola virus belongs to the family of Filoviruses, characterised by filamentous particles. Its particles have a uniform diameter of $80\,nm$ with length up to $14000\,nm$ [13]. As others Filoviruses, it is enveloped, non segmented, negative-stranded RNA with varying morphology. The production of a soluble glycoprotein, also secreted from infected cells, makes it different from the other Mononegavirales [13]. There are five different strains of Ebola virus which have caused several outbreaks mainly on the African continent namely Zaire ebolavirus, Sudan ebolavirus, Cote d'Ivoire ebolavirus, Bundibugyo ebolavirus (Uganda) and Reston ebolavirus which has not yet caused disease in humans [13, 30]. The Zaire Ebola virus species caused the first outbreak in 1976, the outbreaks in Gabon, Republic of Congo, DRC and the actual 2014 outbreak in West Africa [13]. This first strain is the most dangerous one, with a case fatality rate of $60 - 90\%$ [13, 30]. In 1976, the Southern Sudan was affected by the Sudan Ebola virus strain whose case fatality rate was $40 - 60\%$ [13, 30]. In 1994 the third species was discovered, the Cote d'Ivoire Ebola virus, which has only infected one individual up to now [13]. The fourth African Ebola virus strain is the Bundibugyo species found in Equatorial Africa. The Reston Ebola virus species is the last one, found in Philippines for the first time in 1989 and has not been identified in humans, but its emergence in pigs raised important concerns for public health, agricultural and food safety sectors in Philippines [13].

Ebola virus is transmitted to humans by animals. Rodents and bats have always been considered as potential Ebola virus reservoirs [13, 30]. Transmission of the virus into

the human species is done by contacts with the virus through handling of contaminated meat for example. Ebola virus enters the host through mucosal surfaces, breaks or abrasions in the skin [13, 30]. Ebola virus RNA has been detected in semen, genital secretions, skin, body fluids and nasal secretions of infected patients. Ebola is a fluid borne disease and evidence of airborne transmission has not yet been found [17]. The Zaire strain causing the actual outbreak in West Africa only presents 3% of difference from 1976 to 2014. Thus, the virus has not mutated to become airborne or more contagious [17]. Human infections occur after unprotected contacts with infected patients or cadavers [13]. Laboratory exposure through needle stick and blood, and reuse of contaminated needles are the main routes of infection among health care workers [13]. After contamination, symptoms can appear from 2 to 21 days later and the infectious period can last from 4 to 10 days [42]. When the virus gets into a human body, it rapidly replicates and attacks the immune system. So, depending on the state of the infected individual immune system, death can directly follow or recovery after treatment. According to the World Health Organisation (WHO), a suspected case of Ebola disease is any person alive or dead, suffering or having suffered from a sudden onset of high fever and having had contacts with a suspected or confirmed Ebola case, a dead or sick animal and presenting at least three of the following symptoms: headaches, anorexia, lethargy, aching muscles or joints, breathing difficulties, vomiting, diarrhoea, stomach pain, inexplicable bleeding or any sudden inexplicable death [24]. Confirmed cases are the suspected ones who test positive to laboratory Ebola analysis.

Laboratory diagnostic of Ebola virus is done through measurement of host specific immune responses to infection and detection of virus particles. RT-PCR (Reverse Transcription-Polymerase Chain Reaction) and antigen detection ELISA are the primary assays to diagnose an acute infection. Viral antigen and nucleid acid can be detected in blood from 3 to 16 days after onset of symptoms. Direct IgG, IgM ELISAs and IgM capture ELISA are used for antibody detection [13]. A post-Ebola survey results states that 71% of seropositive individuals monitored were asymptomatic [11]. Symptomatic patients with fatal disease develop clinical signs between day 6 and 16 [13]. Asymptomatic or non fatal cases may have fever for several days and improve after $6-11$ days [13, 30]. They mount specific IgM and IgG responses associated with inflammatory response, interleukin β, interleukin 6 and tumour necrosis factor α [13]. There is actually no treatment against Ebola disease and patients who recover from EVD obtain at least a 10 years immunity against the virus strain they were infected by [16]. So, control strategies actually implemented against Ebola disease are mainly meant to stop the transmission chain of

the disease.

1.2 Ebola control strategies

Despite its deadly nature, the control strategies implemented in Liberia has success which was appreciated, and the country was declared Ebola free since May 9, 2015 [47]. A combination of treatment, vaccination trials and non pharmaceutical interventions were implemented in West Africa, to either stop the disease in Guinea and Sierra Leone or avoid a new epidemic in Liberia.

1.2.1 Vaccines and treatments against Ebola

Treatment against EVD mainly consists of providing medical care based on symptomatic therapy to maintain the vital respiratory, cardio-vascular and renal functions [30]. Lots of treatments targeting Ebola virus were undergoing trials in West Africa. FX06 and Zmab had been successfully used in few patients but could not serve for general conclusions on successful treatment outcome [26]. In general, the WHO must review each treatment before it is used against a disease. But, in the context of the Ebola epidemic in West Africa, treatments like amiodarone, atorvastatin combined with irbesartan and clomiphene have been used in emergency without the WHO approval because of the high prevalence of the disease. In addition to these treatments, Favipiravir Fujifilm was tested in Guinea, TKM-100802 was tested in Sierra Leone and ZMapp was tested in Liberia [26]. Vaccines are generally used for prevention purposes and in the case of Ebola disease the following vaccines were in their trial phase in West Africa: ChAd3-ZEBOV, rVSV-ZEBOV, Ad26-EBOV and MVA-EBOV [26]. In 1995, human convalescent blood was used for passive immunisation to treat patients infected by the Zaire Ebola virus. But in vitro studies later showed that antibodies against Ebola have no neutralising activities, so the practice was stopped [30]. For the 2014 Ebola outbreak, trials using convalescent blood plasma were underway in Liberia and Guinea [26]. Because of the limited efficacy of the treatment and vaccines against Ebola disease, non pharmaceutical interventions are the most used.

1.2.2 Non pharmaceutical interventions against Ebola

Since there is actually (as of June 2015) no vaccine or treatment confirmed against Ebola disease, lots of non pharmaceutical control measures are taken at national and international levels to limit the disease incidence. The set of controls against Ebola is di-

vided into pre-epidemic, during the epidemic and post-epidemic measures [25]. The pre-epidemic interventions which help in preventing Ebola disease, comprise the establishment of a viral haemorrhagic fever surveillance system, infection control precautions in health care settings, health promotion programmes and collaboration with wildlife health services [25]. During an Ebola outbreak, the following control measures are suggested to be implemented as given in [25]:

- Coordination and resource mobilization which consist of setting up and training mobile epidemiological surveillance teams, adopting a case definition adapted to the local context of the epidemic, actively searching for cases and investigating each reported case, monitoring each case contacts over a period of 21 days, publishing daily informations, deploying a mobile field laboratory, coordinating human and wildlife epidemic surveillance.
- Behavioural and social interventions which consist of conducting active listening and dialogue with affected communities about behaviours promoted to reduce the risk of new infections, identifying at risk populations, promoting community adherence to the recommended control measures through a culturally sensitive communication, implementing psychological support and assistance.
- Clinical case management is done by introducing standard precautions in health care settings, organising the safe transport of patients from their homes to health-care centres, organising the burials of victims.
- Environmental management consists of monitoring wildlife activities and reinforcing the cooperation between animal health services and public health authorities to stop primary infection and find the source of the disease among animals.

After 42 days without a new Ebola case in a given country, public health authorities declare it Ebola free and the post-epidemic interventions can be implemented. They consist of the resuming of the pre-epidemic interventions to prevent any relapse, the medical follow-up of survivors and monitoring of complications, supervision of male patients whose sperm might still be infectious [25]. Reports on the epidemic should be implemented to address social stigma and exclusion of former patients and health-care workers. This report gives in detail all the activities implemented during the outbreak and the difficulties encountered. It is an important document for future use. A media communication subcommittee is needed at each phase of the epidemic control [25].

1.2.3 Media and communications on Ebola

Communications on Ebola disease are part of the interventions against the disease. In order to control rumours and misinformation by spreading news about the right control measures, a rapid communication between media and health personnel should be conducted at every stage of the epidemic. According to the WHO, an effective media should be reliable, announce early an outbreak, be transparent, respect public concerns and plan in advance [25]. The media tasks during an outbreak are daily collections of information, sharing news related to the latest developments of the disease, reaching the greatest audience in urban and rural areas, documenting the activities of the epidemic management teams with photos and videos [25].

Lots of media are currently in charge of the coverage of the 2014 Ebola outbreak in West Africa, sometimes with an ambiguous impact. Disproportionate airtime allowed to the nine confirmed American cases on *CNN* (Cable News Network), for example, led to a domestic political panic [32]. Media reporting on Ebola have not been sometimes well guided by science in UK (United Kingdoms) and this may has led to public confusion and misinformation [32]. Hopefully, some sources like the Centers for Disease Control and Prevention (CDC), the WHO and the BBCs WhatsApp Ebola service target the most in need by sharing update and science inspired informations [32]. Social media like Twitter or Facebook are also used to raise awareness against Ebola. One of the advantages of using social media is that questions can be ask to experts in the domain in a democratic and transparent way and everyone is given the opportunity to contribute to the solutions' seeking against Ebola [32]. Unbalanced access to social media, proven by the 2103733 tweets about Ebola in USA (United States of America) in October 2014 against only 13480 tweets during the same period in Guinea, Liberia and Sierra Leone combined, raises the problem of access to social media in particular and media in general, on the African continent [32].

1.3 Motivation

The 2014 Ebola disease outbreak has attracted many researchers with its rapid spread and high case fatality rate. It has revealed the weaknesses and breaches of research on Ebola. So, a number of researchers have been investigating Ebola disease dynamics to make projections or to suggest solutions for disease eradication [9, 13, 22]. As well as updated informations on Ebola, all the research innovations have to be made known to the largest possible population through media. Thus, media campaigns are expected

to help affected and infected populations to control Ebola disease. But, in an African context, where social and cultural beliefs deeply affect people's behaviours and confidence in the media, there is a need to investigate the potential role of media campaigns on Ebola transmission. Besides, some research work on the effects of media on diseases dynamics has been done already [38, 44, 46, 48], but none of them has focused on Ebola. This then emphasizes the necessity of exploring the impact of those media on Ebola disease evolution. On the other hand, the control strategies implemented against this 2014 Ebola outbreak and their impact on the disease have been listed in several mathematical works [11, 12, 28]. However, the cost of their implementation has less been raised. In a resource limited region like West Africa, the control measures implementation should take into account the economic and social realities of the affected countries. So, mainly control measures which are affordable and efficacious would actually be implemented, indicating the necessity of studying optimal control of Ebola interventions. This has been done in [40] using an SIR (Susceptible-Infected-Recovered) model with vaccination which does not consider all the disease status of the infected population. In the second part of this project, the first model is extended by considering exposed, infected asymptomatic, hospitalized and dead individuals. Vaccination against Ebola being only in the trial phase in West Africa at the time of writing this thesis, optimal control applied to the extended Ebola disease model with interventions implemented in the field like educational campaigns, active-case finding and pharmaceutical interventions is also done.

1.4 Objectives

The main objective of this project is to study the dynamics of Ebola disease within heterogeneous population in which educational campaigns through media, active-case finding and pharmaceutical interventions are used as control measures against the disease.
The specific objectives are:

- To write a mathematical model including asymptomatic infection and describing the dynamics of Ebola disease within a population whose individuals send Ebola related messages through social media like Twitter.
- To estimate the future number of Ebola cases through fitting the model to data.
- To analyse the stability of the steady states obtained from the model's system of differential equations, in terms of the reproduction number.

- To find conditions under which Ebola disease will persist or die out.
- To fit the model to data from Guinea collected by the WHO field personnel, through some programming tools.
- To apply three time dependent control interventions to Ebola disease, namely educational campaigns, active case-finding and pharmaceutical interventions and evaluate their impact on the disease evolution using Pontryagin's Maximum Principle.

1.5 Significance of the study

This thesis studies the control measures implemented against Ebola virus disease and their effects on the disease evolution. First, the effects of media campaigns on Ebola virus disease transmission is studied to emphasize the necessity of a good collaboration between the media and health care organisations for an early publication of useful informations related to the disease. An optimal control of Ebola virus disease through a set of interventions comprising educational campaigns, active case-finding and pharmaceutical interventions is also done in this thesis. Through their analysis, we show that their long term and joint implementation by organisations like the WHO contributes to the reduction of the prevalence of Ebola virus disease. We also want to highlight the severity of Ebola virus disease and the necessity of sufficient fund to implement the control strategies.

1.6 Overview of the thesis

This thesis is outlined as follows: in Chapter one, the origin and morphology of Ebola virus as well as the description of Ebola virus disease and its different outbreaks are given. Then follows the description of the pharmaceutical and non pharmaceutical interventions implemented against Ebola disease. The motivation of the thesis, its objectives and the significance of the study are also given in this first chapter. Chapter two contains the literature review of media campaigns models and optimal control models. Ebola disease models highlighting interventions against the disease, projections on the disease evolution and focusing on optimal control of the disease are also depicted here. The third chapter formulates a model to study the impact of media campaigns on Ebola transmission with steady states and bifurcation analysis. Numerical simulations describing the evolution of the infected and uninfected populations with time are also

part of this chapter. In the fourth chapter a model for an optimal control of Ebola virus disease is formulated. After the model formulation follows the proof of the existence and the analysis of the optimal control. Numerical simulations helping to make some concluding remarks are done as well in this chapter. The fifth and last chapter dedicated to the general conclusion contains some recommendations on Ebola virus disease control strategies. Some suggestions for the improvement of the study done in this thesis are also given in this chapter.

So, before modelling the dynamics of Ebola virus disease with controls, we look at research work already done on the disease.

Chapter 2

Literature review

2.1 Media campaigns models

A psychological theory suggests that in the course of an epidemic, low levels of worries do not motivate individuals to change their behaviours [27]. To likely increase the perceived efficacy of recommended behaviours and their uptake, the volume of mass media and advertising coverage should be increased. Thus, large and intensive diffusion of media informations on a given disease can play a significant role in the fight against that disease by improving people's reaction to the disease spread [27]. Guided by that psychological theory, some mathematicians are using modelling as a tool to bring scientific proof of the above mentioned theory. Transmissible diseases are privileged targets in this case since limiting the number of new cases is, in some situations, the unique way to stop the disease. One of the greatest tasks in modelling media coverage is to find a mathematical function which will represent the effect of media coverage on individuals receiving informations. The use of media coverage to change people's behaviours when an epidemic is ongoing is not always with guaranteed success. So, the question of the mathematical representation of the impact of media on people's behaviours remains.

Tchuenche and Bauch in [48] chose an exponentially decreasing function $M(t)$ to capture media coverage over time. An $SIRV$ (Susceptible-Infected-Recovered-Vaccinated) model was formulated to represent the dynamics of an infectious disease where media coverage $M(t)$ influences transmission. In this case, $M(t) = \max\{0, aI + b\frac{dI}{dt}\}$ where the positive parameters a and b are intended to capture the phenomenological effects of the total number of cases and the number of cases on media sentiment respectively. Through graphical representations their results show the fading of media signals due to a decline of the incidence and prevalence, which however does not lead to the eradica-

tion of the disease, but contributes to infection control via information dissemination. They concluded that awareness through media and education plays a tremendous role in limiting the spread of an infectious disease. Also, news reporting at rates dependent upon the number of cases and the rate of change in cases can significantly reduce prevalence. In order to improve their model, they suggest the construction of media functions with coefficients graphically determined, the refining of susceptibles class based on behaviour change and the provision of efficacy information coverage. Another mentioned weakness of this model is the limitation of data on media coverage which makes the model less realistic.

Media coverage can have adverse effects on the course of an outbreak. For example, an $SIRV$ deterministic model is used in [46] to assess the impact of media coverage on the transmission dynamics of human influenza. The media effect was due to reporting the number of infections, as well as the number of individuals successfully vaccinated. The effects of the reduction of the contact rate when infectious and vaccinated individuals are reported in the media is measured by the term $\beta_i = \frac{I}{m_I+I}$ for $i = 1, 2$ where m_I reflects the impact of media coverage on contact transmission. Together with the impact of costs that can be incurred, the use of saturated incidence type function in this model led to the conclusion that media amplification of the vaccine efficacy can lead to overconfidence, when individuals take the vaccine as a cure-all, which will increase the endemic equilibrium. Thus, the effects of media coverage on an outbreak of influenza, with a partially effective vaccine may have potentially disastrous consequences in the face of the epidemic. The authors note here that their model was limited by the absence of interdisciplinary research across traditional boundaries of social, natural, medical sciences and mathematics.

Media does not always have negative effects on influenza dynamics. The effects of Twitter on influenza epidemics is described in [38]. A simple SIR (Susceptible-Infected-Recovered) model depicts the disease dynamics and a decreasing exponential term is used to model the media effects on the disease transmission rate. This model proves that social networking tools like Twitter can provide a good real time assessment of the current disease conditions ahead of the public health authorities and thus provide more time for various interventions to contain the epidemic. This model is incomplete because natural birth and death rates have been ignored and in case of an epidemic of long duration, the model will not be valid. The model can be extended by incorporating different age group and geographical factors [38]. Other mathematical models focus on interventions aiming at controlling Ebola epidemics, see for instance [8, 19, 31].

2.2 Optimal control models

The ability to react when an epidemic is declared in a given community strongly depends on social, economical and cultural factors. The best scenario will be to rapidly implement the most effective control strategies to all the susceptibles and infected individuals in the community. However, this is not always the case because of limited resources, which is a common problem in African countries. So, finding the most effective controls with minimum costs, optimal controls, is the best strategy to implement in such cases. The most commonly used control strategies against diseases are treatment, vaccination and educational campaigns. These strategies can be used to cure or prevent the considered diseases. In all cases, reducing the number of infected individuals is the main target. Before their implementation in the field, many optimal control strategies are simulated through modelling in order to preview their impact on the considered disease.

Kar and Jana in [29] did a theoretical study on the mathematical modelling of an infectious disease with application of optimal control in which they used an $SIRV$ (Susceptible-Infected-Recovered-Vaccinated) model. Vaccination and treatment were the controls implemented in this case. First, they considered the simultaneous use of fixed controls and found that they were the best means to use in order to prevent the transformation of the disease into an epidemic. Second, the analysis of the model with time varying controls showed that as long as the implementation of the optimal control theory to the optimal control problem is taken into account, the interventions among different classes and the controls used to the system is important. The limitations of this model reside in the fact that the latent period is assumed to be negligible and which is not always the case for all infectious diseases. Another limitation is the use of non real data which can not help to make conclusions at a general level.

Optimal control was also applied to tuberculosis treatment in [33] where a two-strain tuberculosis model with treatment is considered. Optimal control is used here, to reduce the number of latent and infectious individuals with the resistant strain of tuberculosis. The optimal control results showed the dependence of cost-effective combination of treatment efforts on the population size and costs of implementing treatment controls.

Vaccination is described as well as a disease control strategy in [20], where modelling optimal age-specific vaccination strategies was done. The authors classified individuals as susceptible (S_i), effectively vaccinated but not yet protected (V_i), ineffectively vaccinated (F_i), protected by vaccination (P_i), latent (E_i), infectious in the population

(I_i), hospitalized (J_i), recovered (R_i), and dead (D_i) to make a model that incorporates age-structured transmission dynamics of influenza and to evaluate optimal vaccination strategies in the context of the Spring 2009 A (H1N1) pandemic in Mexico. To minimize the number of infected individuals during the pandemic, they extended previous works on age-specific vaccination strategies to time dependent optimal vaccination policies by solving an optimal control problem with vaccination policies computed under different coverages and different transmissibility levels. Their results showed that when vaccination coverage does not exceed 30%, young adults ($20-39$ years old) and school age children ($6-12$ years old) should be primarily vaccinated. In case of time delay in the vaccination implementation or for higher levels of reproduction number R_0 ($R_0 \geq 2.4$), intensive vaccination protocol within a short period of time is needed in order to reduce the number of susceptible individuals. They also found that optimal age-specific vaccination rates depend on R_0, on the amount of vaccines available and on the timing of vaccination. This model could have been more realistic if it had accounted for asymptomatic cases, high-risk population and constraints imposed by vaccine technologies on delays from pandemic onset to the start of vaccination campaigns [20].

When the economic situation of an affected region is weak or in the absence of effective treatment against a disease, limiting the number of new cases through isolation, quarantine or social distancing is sometimes the unique solution to stop the disease spread. Social distancing coupled to vaccination are optimal control strategies implemented against influenza in [45]. An eight compartments model considering individuals disease status, vaccination status and isolation status was built with the aim of evaluating optimal strategies of vaccination and social distancing for the control of seasonal influenza in the United States of America. They applied optimal control theory to minimize the morbidity and mortality of the disease as well as the economic burden associated to it. Their results suggest, as in [20], that optimal vaccination can be attained when most of the vaccines are administered to preschool-age children and young adults. The authors found that, just at the beginning of the epidemic, intensive efforts were required since the highest vaccination rates were attained for all age groups at that particular period. Concerning social distancing of clinical cases, they found that it tends to last during the whole course of an outbreak and its intensity is the same for all age groups. Besides, in case of higher transmissibility of influenza, they suggested to increase vaccination rather than social distancing of infectious cases. Finally, they recommended to public health authorities to encourage early vaccination and voluntary social distancing of symptomatic cases in order to realise optimal control of seasonal

influenza. They suggested the use of contact reduction measures among clinical cases, which unlike vaccination, can be implemented for a long period of time, as another effective mitigation strategy.

The control strategy used to inform people on the characteristics of a given disease is educational campaigns. Optimal control of an epidemic through educational campaigns was done in [6] by considering two different scenarios. First, susceptibles were encouraged to have protective behaviours through a campaign oriented to decrease the infection rate. Second, infected were stimulated to voluntary quit the infected class through a campaign oriented to increase the removal rate. The author used an SIR model to describe the population dynamics and concluded that if the aim of the campaign is to reach the two above mentioned scenarios, then their implementation should not begin or end at the same time. He mentioned the difficulty in applying theoretic control methods to practical problems in epidemiology, since one doesn't have total knowledge of the state of the epidemics [6]. Education and treatment campaigns are used as control strategies in a smoking dynamics in [51]. A $PLSQ$ (Potential-Light-Smoker-Quit) model with the above mentioned controls describes a quitting smoking scenario. The number of individuals giving up smoking is maximized whereas the number of light and persistent smokers is minimized. Gul Zaman showed an increase in the number of giving up smoking in the optimality system. He used one set of parameters to simulate the system with and the one without control measures. However, to obtain a sampling of possible behaviours of a dynamical system, he suggested to simulate with different sets of parameters. Optimal control was also applied to Ebola disease which was modelled by many researchers.

2.3 Ebola disease models

Since its discovery in 1976 in Kikwit [30], Ebola disease has remained a highly fatal fluid borne disease. Many scientists are using the available tools to help to better understand the disease. The 2014 Ebola outbreak in West Africa, the most deadly Ebola outbreak ever, raised important scientific concern of the disease. This led to the implementation of almost all the existing control strategies against the disease. To help national and international stakeholders on the Ebola situation in west Africa, scientific research is still being carried out to stop the epidemic and any future outbreak. Thus, to raise awareness against the high transmission of Ebola virus, the total number of Ebola cases which was 3685 in August 2014 was predicted to reach 21000 in September 2014 through the use of

EbolaResponse modelling tool in [9]. But, considering 50% of asymptomatic infection in [11], the number of Ebola cases was reduced of 50% in projections, suggesting the importance of investigations of asymptomatic immunity against Ebola disease. This can be done by the joint use of serological testing and intervention efforts in West Africa. To avoid the spread of Ebola disease out of the West African boundaries, strategies for containing Ebola in that part of the African continent have been listed and studied in [28]. A stochastic model of Ebola transmission was set to assess the effectiveness of containment strategies. From the conclusions in [28], a joint approach of case isolation, contact-tracing with quarantine and sanitary funeral practices should be urgently implemented in the case of an epidemic outbreak. The authors here admit that the effectiveness of hospital-based interventions depends on treatment center capacity and admission rate and their model do not explicitly account for that. This then constitutes a weakness of their model which is also limited by the scarcity of data on the previous and the 2014 Ebola outbreaks. The impact of interventions on the Ebola epidemic in Sierra Leone and Liberia in 2014 is evaluated in [12]. A six compartments model describing the dynamics of Ebola disease with control measures such as contact tracing, infection control and pharmaceutical interventions is considered. The analysis of the model showed that increased contact tracing coupled to improved infection control could have insignificant impact on the number of Ebola cases. Pharmaceutical interventions had a less influence on the course of the epidemic. As limitations to their model, the authors cited the delay in the time series model due to the use of data on Ebola cases at the time of their reporting and not at the time of the onset of the disease. They also stressed the inaccuracy of the model and its data, due to the fact that the manuscript was written during the epidemic.

Optimal control of the 2014 Ebola outbreak with vaccination as a control measure is done in [40]. An SIR (Susceptible-Infected-Recovered) model that describes the disease dynamics within a population has optimal control incorporated to study the impact of vaccination on the spread of Ebola virus. The analysis of the model showed that vaccination helped in reducing the number of infected individuals in a short period of time. The authors suggested to extend the model by investigating the effects of impulsive vaccination or the impact of treatment combined to quarantine of Ebola infected individuals on the disease evolution.

In this research project, the models developed will focus on the impact of control measures on Ebola disease dynamics. The first control measure studied in this thesis investigates the use of social media to spread messages against Ebola virus disease, which

is an innovation since similar topic has not been found in publications at the time of writing the thesis. Media campaigns against Ebola disease are sent through media and particularly social media like Twitter or Facebook. Their effects on the disease evolution are studied in the following chapter.

Chapter 3

Impact of media campaigns on Ebola transmission

3.1 Introduction

The world has faced one of the most devastating Ebola virus disease (EVD) epidemic ever since December 2013, when the epidemic started in a small village in Guinea. This deadly disease is caused by a virus called Ebola, which was discovered in the Democratic Republic of Congo in 1976 near a river called Ebola. This virus lives in animals like bats and primates, mostly found in Western and Central Africa. The virus can move from animals to humans when an infectious animal has contact with a human and contamination is also possible among animals. Contamination can occur among humans when they have non protected contacts with an infectious individual's fluids like faeces, vomit, saliva, sweat and blood [2].

Symptoms can appear after 2 to 21 days following the contamination and the infectious period can last from 4 to 10 days [42]. According to the World Health Organisation (WHO), a suspected case of EVD is any person alive or dead, suffering or having suffered from a sudden onset of high fever and having had contacts with a suspected or confirmed Ebola case, a dead or sick animal and at least three of the following symptoms: headaches, anorexia, lethargy, aching muscles or joints, breathing difficulties, vomiting, diarrhoea, stomach pain, inexplicable bleeding or any sudden inexplicable death [24]. Confirmed cases of EVD are individuals who would have tested positive for the virus antigen either by detection of virus RNA by Reverse Transcriptase Polymerase Chain Reaction or by detection of IgM antibodies directed against Ebola [24].

Ebola seropositive individuals can either be asymptomatic or symptomatic. A post-Ebola survey result states that 71% of seropositive individuals monitored were asymptomatic [11]. Symptomless EVD patients have a low infectivity due to their very low viral load whereas the symptomatic cases transmit the disease through their fluids [4]. There is actually no treatment against EVD. Oral rehydratation salt and pain relief are given to infected symptomatic persons and those who recover from EVD obtain at least a 10 years immunity against the virus strain they were infected by.

Media campaigns have always been a key role in fighting diseases of such an extent. They disseminate oral or written disease related informations even to the most remote areas of a given country. The most used means of information about EVD are televisions, radios and new information technologies linked to internet such as social media. Thus people can receive and even send messages related to EVD at any time especially the most affected individuals. The WHO and the Centers for Disease Control and Prevention (CDC) are the most active in sending reliable information on EVD [14, 25]. At a national or local level, governments of the affected countries have put in place hotlines to receive free calls from people in need of assistance when they face an Ebola case. Some mobile applications like the Ebola Prevention App (EPA), which is a free mobile application displaying the affected areas, preventive measures and up to date informations on EVD around the world have been developed [21]. Also, short messages of at most 140 characters called tweets can be sent through the social network Twitter [38].

To better understand the dynamics of EVD and make some predictions, many areas of specialisations are joining their efforts to find efficient responses to issues raised by that disease. In the domain of mathematics and public health, modelling has always been used as a tool for that purpose and that is why we intend to formulate a model in the first part of this research project which will evaluate the effects of media campaigns on EVD transmission.

3.2 Model formulation

A deterministic model is used to describe the population dynamics in this case and its five independent compartments are susceptible (S), exposed (E), infected asymptomatic (I_a), infected symptomatic (I_s) and recovered (R). Only the Zaire Ebola virus strain causing the actual outbreak in West Africa will be considered. Recruitment into the sus-

ceptibles class is done through birth or migration at a constant rate Λ and susceptible individuals become exposed after unsafe contact with Ebola virus. The population of susceptibles is decreased also by natural death at a rate μ and EVD related messages are sent by individuals from that class at a rate α_1. After contamination, susceptibles move to compartment E and Taking $\frac{1}{\gamma}$ as the incubation period, individuals leave the exposed compartment either at a rate γ to develop symptoms or because they die naturally at a rate μ. The exposed send Ebola related messages at the rate α_2. After the incubation period, a proportion $(1-p)$ of exposed individuals can develop symptoms and become infected symptomatic. The infected symptomatic class is diminished by natural death at a rate μ, EVD related death at a rate σ or recovery at a rate δ_2. Besides, symptomatic send messages related to the disease at a rate α_4. But a proportion p of the exposed do not develop symptoms and are infected asymptomatic who can naturally die at a rate μ, recover at a rate δ_1 or send messages at a rate α_3. However, some of those initially declared asymptomatic may develop symptoms after 21 days and become symptomatic at a rate θ. Recovered individuals can only quit the compartment via natural death at a rate μ and they send messages at a rate α_5. Messages are assumed to get outdated at a rate ω. The study is made over a relatively large period so that those who recover from EVD gain a permanent immunity against the strain. The flow diagram is presented on Figure 3.1.

Let N be the total size of the population, so that

$$N(t) = S(t) + E(t) + I_a(t) + I_s(t) + R(t).$$

We set $S(0) = S_0, E(0) = E_0, I_a(0) = I_{a0}, I_s(0) = I_{s0}$ and $R(0) = R_0$ as the initial values of each of the state variables S, E, I_a, I_s and R, all assumed to be positive.

After receiving tweets or messages, the population decides on the means of preventing or recovering from the disease when it is possible. The behaviour adopted by individuals after receiving media campaigns will help in evaluating those campaigns efficacy. The general objective of media campaigns against a disease is to increase the population awareness of the disease and correct misperceptions about how it is spread, how it is and is not acquired [5]. The efficacy of messages sent through media is thus their ability to produce that intended result. We assume here that media campaigns primarily target the transmission process and their time dependent efficacy will be denoted $M(t), \forall t \geqslant 0$ with $0 < M(t) \leq 1$. We also assume here that transmission is a result of direct contact

with Ebola symptomatic patients or their fluids and asymptomatic individuals do not transmit the disease [1]. The reduction factor is a function of $M(t)$ and denoted

$$f(t) = (1 - M(t)), \quad \forall t \geqslant 0.$$

The force of infection is given by

$$\lambda(t) = \beta c(1 - M(t))\frac{I_s(t)}{N(t)}, \quad \forall t \geqslant 0$$

where β is the probability that a contact will result in an infection and c the number of contacts between susceptibles and the diseased. The model does not include the influence of EVD death in the transmission process. We make a simplifying assumption here that the effects of disease related mortality is captured through the sending of messages by the living.

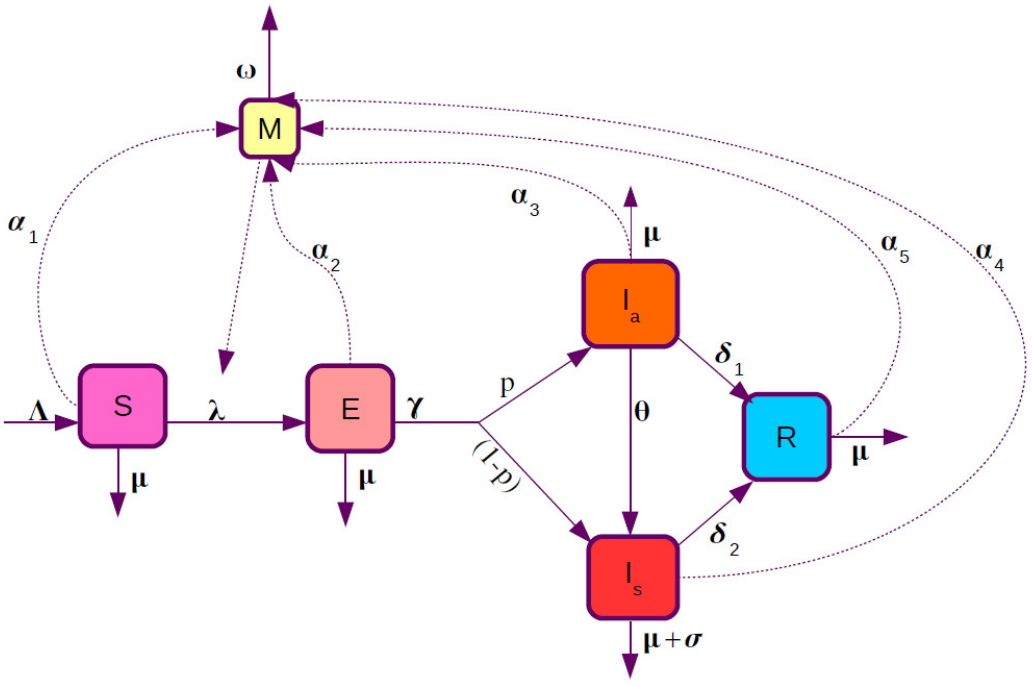


Figure 3.1: Flow diagram for EVD

3.2.1 Model equations

Following the model assumptions and the description of the flow diagram, the system of differential equations describing the dynamics of the model is as follows :

$$\frac{dS}{dt} = \Lambda - (\lambda + \mu)S, \tag{3.2.1}$$
$$\frac{dE}{dt} = c\beta(1-M)\frac{I_s}{N}S - (\gamma + \mu)E, \tag{3.2.2}$$
$$\frac{dI_a}{dt} = p\gamma E - (\mu + \theta + \delta_1)I_a, \tag{3.2.3}$$
$$\frac{dI_s}{dt} = (1-p)\gamma E + \theta I_a - (\delta_2 + \sigma + \mu)I_s, \tag{3.2.4}$$
$$\frac{dR}{dt} = \delta_1 I_a + \delta_2 I_s - \mu R, \tag{3.2.5}$$
$$\frac{dM}{dt} = \alpha_1 S + \alpha_2 E + \alpha_3 I_a + \alpha_4 I_s + \alpha_5 R - \omega M. \tag{3.2.6}$$

3.3 Model properties and analysis

3.3.1 Existence and uniqueness of solutions

The right hand side of system (3.2.1)-(3.2.6) is made of Lipschitz continuous functions since they describe the size of a population. According to Picard's existence Theorem, with given initial conditions, the solutions of our system exist and they are unique.

Theorem 3.3.1. *The system makes biological sense in the region*

$$\Omega = \{(S(t), E(t), I_a(t), I_s(t), R(t), M(t)) \in R^6 : N(t) \leqslant \frac{\Lambda}{\mu}, 0 < M(t) \leqslant 1\}$$

which is attracting and positively invariant with respect to the flow of system (3.2.1)-(3.2.6).

Proof. By adding equations (3.2.1) to equation (3.2.5) we have :

$$\frac{dN}{dt} = \Lambda - \mu N - \sigma I_s,$$

which implies

$$\frac{dN}{dt} \leqslant \Lambda - \mu N. \tag{3.3.1}$$

Using Corollary 3.3.4 we obtain

$$0 \leqslant N(t) \leqslant \left(N(0) - \frac{\Lambda}{\mu}\right)\exp(-\mu t) + \frac{\Lambda}{\mu}, \quad \forall\ t \geqslant 0.$$

We have $\lim_{t\to\infty} N(t) < \frac{\Lambda}{\mu}$ when $N(0) \leqslant \frac{\Lambda}{\mu}$. However, if $N(0) \geqslant \frac{\Lambda}{\mu}$, $N(t)$ will decrease to $\frac{\Lambda}{\mu}$. So $N(t)$ is thus a bounded function of time. Together with M which is already bounded, we can say that Ω is bounded and at limiting equilibrium $\lim_{t\to\infty} N(t) = \frac{\Lambda}{\mu}$. Besides, any sum or difference of variables in Ω with positive initial values will remain in Ω or in a neighbourhood of Ω. Thus Ω is positively invariant and attracting with respect to the flow of system (3.2.1)-(3.2.6). □

3.3.2 Positivity of solutions

Theorem 3.3.2. *The existing solutions of our system* (3.2.1)-(3.2.6) *are all positive.*

Proof. From (3.2.1) we have

$$\frac{dS}{dt} = \Lambda - (\lambda(t) + \mu)S, \forall t \geqslant 0, \tag{3.3.2}$$

which implies

$$\frac{dS}{dt} \geqslant -(\lambda(t) + \mu)S, \forall t \geqslant 0. \tag{3.3.3}$$

Solving $\frac{dS}{dt} = -(\lambda(t) + \mu)S$ yields

$$S(t) = S(0) \exp\Big[\int_0^t \lambda(u)\, du\Big] \exp(-\mu)t. \tag{3.3.4}$$

Using (4.3.2) and (4.3.5) we obtain

$$S(t) \geqslant S(0) \exp\Big[\int_0^t \lambda(u)\, du\Big] \exp(-\mu)t \tag{3.3.5}$$

which is positive given that $S(0)$ is also positive.
Similarly, from (3.2.2) we have

$$\frac{dE}{dt} \geqslant -(\gamma + \mu)E \quad \forall\, t \geqslant 0,$$

so that

$$E(t) \geqslant E(0) \exp[-(\gamma + \mu)]t,$$

thus shows that $E(t)$ is positive since $E(0)$ is also positive.
Similarly from (3.2.3) we can write

$$\frac{dI_a}{dt} \geqslant -(\mu + \theta + \delta_1)I_a \quad \forall t \geqslant 0,$$

from which we obtain

$$I_a(t) \geqslant I_a(0)\exp[-(\mu+\theta+\delta_1)]t.$$

Thus I_a is positive since $I_a(0)$ is positive.
The remaining equations yield

$$I_s(t) \geqslant I_s(0)\exp -[(\mu+\sigma+\delta_2)]t,$$

$$R(t) \geqslant R(0)\exp(-\mu t)$$

and

$$M(t) \geqslant M(0)\exp(-\omega t).$$

So $I_s(t), R(t)$ and $M(t)$ are all positive for positive initial conditions. Thus all the state variables are positive. □

3.3.3 Steady states analysis

Our model has two steady states: the disease free equilibrium (DFE) which describes the total absence of EVD in the studied population and the endemic equilibrium (EE) which exists at any positive prevalence of EVD in the population. This section is dedicated to the study of local and global stability of these steady states.

3.3.4 The disease free equilibrium and R_M

At the disease free equilibrium $(S, E, I_a, I_s, R, M) = (S^*, 0, 0, 0, 0, M^*)$. The resolution of the following system

$$-\mu S^* + \Lambda = 0,$$
$$\alpha_1 S - \omega M^* = 0,$$

yields

$$S^* = \frac{\Lambda}{\mu} \text{ and } M^* = \frac{\Lambda\alpha_1}{\omega\mu}.$$

To compute the media campaigns reproduction number R_M we use the next generation method comprehensively discussed in [10]. The renewal matrix $\mathcal{F}$ and transfer matrix $\mathcal{V}$ at DFE are:

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & c\beta(1-M^*) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} Q_1 & 0 & 0 \\ -\gamma p & Q_2 & 0 \\ (p-1)\gamma & -\theta & Q_3 \end{bmatrix}$$

where

$$Q_1 = \gamma + \mu,\ Q_2 = \mu + \theta + \delta_1 \quad \text{and} \quad Q_3 = \delta_2 + \sigma + \mu.$$

The media campaigns reproduction number R_M is the spectral radius of the matrix $\mathcal{F}\mathcal{V}^{-1}$ and is given by

$$R_M = \frac{c\beta\gamma(1-M^*)}{Q_1Q_2Q_3}\Big[p\theta + (1-p)Q_2\Big].$$

We can write $R_M = R_1 + R_2$ for elucidation purpose with

$$R_1 = \Big(\frac{pc\beta(1-M^*)}{Q_3}\Big)\Big(\frac{\gamma}{Q_1}\Big)\Big(\frac{\theta}{Q_2}\Big), \quad R_2 = \Big(\frac{c\beta(1-p)(1-M^*)}{Q_3}\Big)\Big(\frac{\gamma}{Q_1}\Big).$$

Note here that $\frac{1}{Q_3}$ is the duration of infectivity for the symptomatic, $\frac{\theta}{Q_2}$ the probability that an individual in I_a moves to I_s and $\frac{\gamma}{Q_1}$ the probability that an individual in E moves either to I_a or I_s. Thus, the media campaigns reproduction number is a sum of secondary infections due to the infectious individuals (R_1) in I_s and the asymptomatic individuals who become infectious (R_2). We can notice the reduction factor $0 \leqslant (1-M^*) < 1$ which represents the attenuating effect of media campaigns on the future number of EVD cases.

3.3.4.1 Local and global stability

The description of the DFE stability is given below.

Theorem 3.3.3. *The DFE is locally stable whenever $R_M < 1$ and unstable otherwise.*

Proof. In other to prove the local stability of the DFE, we show that the Jacobian matrix of the system (3.2.1) - (3.2.6) at the DFE has negative eigenvalues. The Jacobian matrix J of the linearised system is:

$$J = \begin{bmatrix} -\mu & 0 & 0 & -c\beta(1-M^*) & 0 & 0 \\ 0 & -Q_1 & 0 & c\beta(1-M^*) & 0 & 0 \\ 0 & p\gamma & -Q_2 & 0 & 0 & 0 \\ 0 & (1-p)\gamma & \theta & -Q_3 & 0 & 0 \\ 0 & 0 & \delta_1 & \delta_2 & -\mu & 0 \\ \alpha_1 & \alpha_2 & \alpha_3 & \alpha_4 & \alpha_5 & -\omega \end{bmatrix}.$$

The characteristic equation of J is given by :

$$(\zeta+\mu)^2(\zeta+\omega)(\zeta^3+a_1\zeta^2+a_2\zeta+a_3)=0 \tag{3.3.6}$$

with

$$\begin{aligned}
a_1 =& Q_1+Q_2+Q_3,\\
a_2 =& c\beta\gamma(1-M^*)(p-1)+Q_1Q_2+Q_3Q_2+Q_1Q_3,\\
=& Q_1Q_3\Big(1-R_2\Big)+Q_1Q_2+Q_3Q_2,\\
a_3 =& Q_1Q_2Q_3[1-\frac{c\beta\gamma(1-M^*)}{Q_1Q_2Q_3}\big(p\theta+(1-p)Q_2\big)].\\
=& Q_1Q_2Q_3(1-R_M).
\end{aligned}$$

Since $-\mu$ (twice) and $-\omega$ are negative roots of the characteristic polynomial (3.3.6), we use Routh-Hurwitz criterion to show that the remaining polynomial

$$\zeta^3+a_1\zeta^2+a_2\zeta+a_3=0$$

has negative real roots.
The first condition for these criteria to be used is that a_3 must be positive and clearly when $R_M<1$, a_1, a_2 and a_3 are all positive. In addition, $a_1a_2-a_3$ must be positive to have negative real roots for the polynomial. We thus have

$$a_1a_2-a_3=\ Q_1Q_3(Q_2+Q_3)(1-R_2)+Q_1Q_2+Q_3Q_2Q_1R_M,$$

so $a_1a_2-a_3>0$ since $R_2<R_M<1$. The necessary and sufficient condition for the Jacobian matrix J to have negative roots is that the reproduction number is less than one. From the Routh-Hurwitz stability criterion, we can conclude that the DFE is locally asymptotically stable when $R_M<1$ and unstable for $R_M>1$. □

Corollary 3.3.4. *Let x_0, y_0 be real numbers, $I=[x_0,+\infty)$ and $a,b\in C(I)$. Suppose that $y\in C^1(I)$ satisfies the following inequality*

$$y'(x)\leqslant a(x)y(x)+b(x),\ x\geqslant x_0,\ y(x_0)=y_0. \tag{3.3.7}$$

Then

$$y(x) \leqslant y_0 \exp\left(\int_{x_0}^{x} a(t)\,dt\right) + \int_{x_0}^{x} b(s) \exp\left(\int_{s}^{x} a(t)\,dt\right) ds,\ x \geqslant x_0. \tag{3.3.8}$$

If the converse inequality holds in (3.3.7)*, then the converse inequality holds in* (3.3.8) *too.*

3.3.5 Existence and stability of the endemic equilibrium

In this section we show the existence of the endemic equilibrium (EE). We denote the endemic equilibrium by $(S^{**}, E^{**}, I_a^{**}, I_s^{**}, R^{**}, M^{**})$. At equilibrium,

$$\begin{aligned}
\Lambda - (\lambda + \mu)S &= 0, && (3.3.9)\\
c\beta(1-M)\frac{I_s}{N}S - (\gamma+\mu)E &= 0, && (3.3.10)\\
p\gamma E - (\mu + \theta + \delta_1)I_a &= 0, && (3.3.11)\\
(1-p)\gamma E + \theta I_a - (\delta_2 + \sigma + \mu)I_s &= 0, && (3.3.12)\\
\delta_1 I_a + \delta_2 I_s - \mu R &= 0, && (3.3.13)\\
\alpha_1 S + \alpha_2 E + \alpha_3 I_a + \alpha_4 I_s + \alpha_5 R - \omega M &= 0. && (3.3.14)
\end{aligned}$$

Thus, from equation (3.3.9) we have

$$S^{**} = \frac{1}{\lambda^{**} + \mu} Q_1 Q_2 Q_3.$$

From equation (3.3.10) we have

$$E^{**} = \frac{\lambda^{**}}{(\lambda^{**} + \mu)} Q_2 Q_3,$$

from equation (3.3.11) we have

$$I_a^{**} = \frac{p\gamma\lambda^{**}}{(\lambda^{**} + \mu)} Q_3,$$

from equation (3.3.12) we have

$$I_s^{**} = \frac{\gamma\lambda^{**}\left[p\theta + Q_2(1-p)\right]}{(\lambda^{**} + \mu)},$$

from equation (3.3.13) we have

$$R^{**} = \frac{\gamma\lambda^{**}\Big[p(Q_3\delta_1 + \theta\delta_2) + Q_2\delta_2(1-p)\Big]}{\mu(\lambda^{**}+\mu)}$$

and from equation (3.3.14) we have

$$M^{**} = \frac{1}{\mu\omega(\lambda^{**}+\mu)}(\phi_1 + \phi_2\lambda^{**})$$

where

$$\lambda^{**} = \beta c(1-M^{**})\frac{I_s^{**}}{N^{**}},$$
$$\phi_1 = \mu Q_1 Q_2 Q_3 \alpha_1$$

and

$$\phi_2 = \gamma(\mu\alpha_4 + \alpha_5\delta_2)(p\theta + (1-p)Q_2) + Q_3\Big(\mu(Q_2\alpha_2 + p\gamma\alpha_3) + p\gamma\alpha_5\delta_1\Big).$$

Set $P(\lambda^{**}) = \lambda^{**} - \beta c(1-M^{**})\frac{I_s^{**}}{N^{**}}$. By replacing M^{**}, I_s^{**} and N^{**} by their values expressed as functions of λ^{**} and by setting

$$P(\lambda^{**}) = 0$$

we obtain the following equation:

$$\Lambda\lambda^{**}[(\nu_2(\lambda^{**})^2 + \nu_1\lambda^{**} + \nu_0)] = 0 \tag{3.3.15}$$

where

$$\begin{cases} \nu_0 &= \omega Q_1 Q_2 Q_3 \mu(1-R_M), \\ \nu_1 &= \mu\omega Q_1^2 Q_2^2 Q_3^2 + \omega Q_1 Q_2 Q_3 \Sigma, \\ \nu_2 &= \omega Q_1 Q_2 Q_3\Big[\gamma(\mu+\delta_2)(p\theta + (1-p)Q_2) + \mu(Q_3(Q_2 + p\gamma(\mu+\delta_1)))\Big] > 0, \end{cases} \tag{3.3.16}$$

with $\Sigma = \Big[-\gamma(c\beta-\mu)(p\theta + Q_2(1-p)) + \mu\phi_2(p\gamma + Q_2)Q_3\Big]\mu + \gamma\mu\Big[pQ_3\delta_1 + (p\theta + Q_2(1-p)\delta_2)\Big] + c\beta\gamma\Lambda\Big[p\theta + (1-p)Q_2\Big]$.

From equation (3.3.15), $\lambda^{**} = 0$ corresponds to the DFE discussed in the previous section. The signs of the solutions of the quadratic equation

$$\nu_2(\lambda^{**})^2 + \nu_1\lambda^{**} + \nu_0 = 0 \tag{3.3.17}$$

are given in the Table 3.1 below.

	$\nu_2 > 0$			
	$\nu_1 > 0$		$\nu_1 < 0$	
	$\nu_0 > 0\,(R_M < 1)$	$\nu_0 < 0\,(R_M > 1)$	$\nu_0 > 0\,(R_M < 1)$	$\nu_0 < 0\,(R_M > 1)$
λ_1^{**}	$-$	$-$	$+$	$-$
λ_2^{**}	$-$	$+$	$+$	$+$

Table 3.1: Roots signs.

From Table 3.1, we notice that for the existence and uniqueness of the endemic equilibrium, ν_0 must be negative since ν_1 and ν_2 are always positive. This is only possible if $R_M > 1$. Thus we have the following theorem on the existence of the endemic equilibrium:

Theorem 3.3.5.

- *If* $R_M > 1$ *equation* (3.3.17) *has a unique positive solution and hence system* (3.2.1)-(3.2.6) *has a unique endemic equilibrium.*
- *If* $R_M^c < R_M < 1$ *and* $\nu_1 < 0$, *the roots* λ_1^{**} *and* λ_2^{**} *are both positive, hence system* (3.2.1)-(3.2.6) *admits two endemic equilibria.*
- *If* $R_M^c = R_M$ *then* (3.3.17) *has a repeated positive root, hence a unique endemic equilibrium for system* (3.2.1)-(3.2.6).
- *If* $0 < R_M < R_M^c$ *the system* (3.2.1)-(3.2.6) *does not admit any endemic equilibrium and hence only the DFE exists.*

Provided $\nu_1 < 0$, the existence of two endemic equilibria for $R_M < 1$ suggests the existence of a backward bifurcation since the DFE exists also in that particular domain. The coexistence of DFE and endemic equilibrium when $R_M < 1$ is a well known characteristic of a backward bifurcation described in [23]. Thus,

there exists a critical value of R_M called here R_M^c for which there is a change in the qualitative behaviour of our model.
At the bifurcation point, there is an intersection between the line $R_M = R_M^c$ and the graph of $P(\lambda^{**})$. Thus the discriminant Δ is equal to zero at $R_M = R_M^c$, which mathematically is

$$\nu_1^2 - 4\omega Q_1 Q_2 Q_3 \mu (1 - R_M^c)\nu_2 = 0$$

from which

$$R_M^c = 1 - \frac{\nu_1^2}{4\psi\nu_2}.$$

Theorem 3.3.6. *Given that* $R_M^c = 1 - \dfrac{\nu_1^2}{4\psi\nu_2}$, *with* $\psi = \omega Q_1 Q_2 Q_3 \mu$, ν_1 *and* ν_2 *are defined in* (3.3.16) , *the DFE is globally asymptotically stable whenever* $R_M < R_M^c$.

Proof. To show the global stability of the DFE we use the Invariance Principle of Lassale [43]. Let us set $V(t) = E(t) + I_a(t) + I_s(t)$ as our Lyapunov function.

$$\begin{aligned} V(t) &> 0 \qquad \text{since} \qquad E(t) > 0,\ I_a(t) > 0,\ I_s(t) > 0, \forall t > 0. \\ V(t) &= 0 \qquad \text{if} \qquad E(t) = I_a(t) = I_s(t) = 0 \,(\text{at } DFE). \end{aligned}$$

Thus V is a positive definite function at the DFE.
From equation (3.2.6) we have

$$\frac{dM}{dt} \geqslant \alpha_1 S - \omega M.$$

By applying Corollary 3.3.4 we have

$$M(t) \geqslant M(0)\exp\left(\int_0^t (-\omega)\,du\right) + \int_0^t \alpha_1 S \exp\left(\int_z^t (-\omega)\,dv\right) dz,\ \forall t \geqslant 0$$

which yields

$$M(t) \geqslant \exp(-\omega t)\left(M(0) - \frac{\alpha_1 S}{\omega}\right) + \frac{\alpha_1 S}{\omega}. \tag{3.3.18}$$

Before the disease is spread, we assume that M is at the steady state level. So $M(0) = \dfrac{\alpha_1 S}{\omega}$ which is equivalent to $M(0) = M^*$ and (3.3.18) will give

$$M(t) \geqslant \frac{\alpha_1 S}{\omega}.$$

Together with the assumption $0 < M \leqslant 1$ we thus have

$$M^* \leqslant M(t) \leqslant 1.$$

The derivative of V is given by

$$\begin{aligned}\dot{V} &= \dot{E} + \dot{I}_a + \dot{I}_s, \\ &= \Big(c\beta(1-M)\frac{S}{N} - Q_3\Big)I_s + (\gamma - Q_1)E + (\theta - Q_2)I_a.\end{aligned}$$

Since $S \leqslant N$, $\dfrac{S}{N} \leqslant 1$ and in addition $M(t) \geqslant M^*$. We thus have

$$\dot{V} \leqslant [c\beta(1-M^*) - Q_3]I_s + (\gamma - Q_1)E + (\theta - Q_2)I_a. \tag{3.3.19}$$

At equilibrium,

$$\begin{aligned} c\beta(1-M)\frac{I_s}{N}S - (\gamma+\mu)E &= 0, && (3.3.20)\\ p\gamma E - (\mu+\theta+\delta_1)I_a &= 0, && (3.3.21)\\ (1-p)\gamma E + \theta I_a - (\delta_2+\sigma+\mu)I_s &= 0. && (3.3.22)\end{aligned}$$

From equation (3.3.21) we have

$$E = \frac{Q_2}{p\gamma}I_a. \tag{3.3.23}$$

From equation (3.3.22) we have

$$I_s = \frac{(p\theta + (1-p)Q_2)}{pQ_3}I_a. \tag{3.3.24}$$

By plugging (3.3.23) and (3.3.24) in (3.3.19) we obtain after simplifications

$$\begin{aligned}\dot{V} &\leqslant \frac{-Q_1Q_2}{p}\Big[1 - c\beta\gamma(1-M^*)\frac{(p\theta+(1-p)Q_2)}{Q_1Q_2Q_3}\Big]I_a, \\ &\leqslant \frac{-Q_1Q_2}{p}\Big[1 - R_M\Big]I_a, \\ &\leqslant \frac{-Q_1Q_2Q_3}{\Big[p\theta+(1-p)Q_2\Big]}(1-R_M)I_s.\end{aligned}$$

Thus $\dot{V} \leqslant 0$ when $R_M \leqslant 1$ and particularly, $\dot{V} = 0$ only if $E = I_a = I_s = 0$. Because the largest invariant set for which $\dot{V} = 0$ in Ω is the DFE and $\dot{V} \leqslant 0$ if $R_M \leqslant 1$, by using the Invariance Principle of Lassale [43] we can conclude that the DFE is globally asymptotically stable for $R_M \leqslant 1$. Together with the existence of a backward bifurcation, one can say that for $R_M < R_M^c$ the DFE is globally stable. □

Remark 3.3.7.

$$\begin{cases} 0 < R_M < R_M^c & \text{the } DFE \text{ is globally stable,} \\ R_M^c < R_M < 1 & \text{the } DFE \text{ is locally stable and two endemic equilibria exist} \\ & \text{with one which is stable and the other one unstable.} \end{cases}$$

3.4 Local stability of endemic equilibrium

The DFE and EE both describe different qualitative behaviours of our epidemic. Let us set $\phi = c\beta(1 - M^*)$ as our bifurcation parameter, so that for

$$R_M = 1, \qquad \phi = \phi^* = \frac{Q_1 Q_2 Q_3}{\gamma(p\theta + (1-p)Q_2)}.$$

In order to describe the stability of the endemic equilibrium, we will use the theorem, remark and corollary in [7] which are based on the Centre Manifold Theory.

Theorem 3.4.1. *Consider a general system of ordinary differential equations with a parameter ϕ:*

$$\frac{dx}{dt} = f(x, \phi), \qquad f : \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R}^n \quad \text{and} \quad f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}). \tag{3.4.1}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (3.4.1) for all values of the parameter ϕ, that is $f(0, \phi) \equiv 0$ for all ϕ.

Assume

$A1 : A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0) \right)$ *is the linearisation matrix of System (3.4.1) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;*

A2: Matrix A has a non negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue. Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \quad b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0).$$

The local dynamics of (3.4.1) *around* 0 *are totally determined by a and b.*

1. $a > 0, b > 0$. *When* $\phi < 0$ *with* $\mid \phi \mid \ll 1$, 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$, 0 *is unstable and there exists a negative and locally asymptotically stable equilibrium;*

2. $a < 0, b < 0$. *When* $\phi < 0$ *with* $\mid \phi \mid \ll 1$, 0 *is unstable; when* $0 < \phi \ll 1$, 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium;*

3. $a > 0, b < 0$. *When* $\phi < 0$ *with* $\mid \phi \mid \ll 1$, 0 *is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$, 0 *is stable, and a positive unstable equilibrium appears;*

4. $a < 0, b > 0$. *When* ϕ *changes from negative to positive,* 0 *changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Corollary 3.4.2. *When* $a > 0$ *and* $b > 0$, *the bifurcation at* $\phi = 0$ *is subcritical or backward.*

For the model (3.2.1)-(3.2.6), the DFE (E_0) is not equal to zero. According to Remark 1 in [7], we notice that if the equilibrium of interest in Theorem (3.4.1) is a non-negative equilibrium x_0, then the requirement that w is non negative in Theorem (3.4.1) is not necessary. When some components in w are negative, one can still apply Theorem (3.4.1) on condition that:

$$\begin{cases} w(j) > 0 & \text{if } x_0(j) = 0, \\ \text{if } x_0(j) > 0, & w(j) \text{ does not need to be positive,} \end{cases}$$

where $w(j)$ and $x_0(j)$ denote the jth component of w and x_0 respectively.

First, let us rewrite system (3.2.1)-(3.2.6) introducing

$$S = x_1,\ E = x_2,\ I_a = x_3,\ I_s = x_4,\ R = x_5,\ M = x_6$$

and

$$\dot{S} = f_1,\ \dot{E} = f_2,\ \dot{I}_a = f_3,\ \dot{I}_s = f_4,\ \dot{R} = f_5,\ \dot{M} = f_6.$$

The equilibrium of interest here is the DFE denoted $E_0 = (S^*, 0, 0, 0, 0, M^*)$ and the bifurcation parameter is ϕ^*.
The linearisation matrix A of our model at (E_0, ϕ^*) is

$$A = \begin{bmatrix} -\mu & 0 & 0 & -\phi^* & 0 & 0 \\ 0 & -Q_1 & 0 & \phi^* & 0 & 0 \\ 0 & p\gamma & -Q_2 & 0 & 0 & 0 \\ 0 & (1-p)\gamma & \theta & -Q_3 & 0 & 0 \\ 0 & 0 & \delta_1 & \delta_2 & -\mu & 0 \\ \alpha_1 & \alpha_2 & \alpha_3 & \alpha_4 & \alpha_5 & -\omega \end{bmatrix}.$$

The eigenvalues of A are:
$-\mu$ (twice), $-\omega$, 0 and the roots of the polynomial (3.4.2) below

$$Q(\varsigma) = a_0\varsigma^2 + a_1\varsigma + a_2 \tag{3.4.2}$$

where

$$\begin{aligned} a_0 &= p\theta + Q_2(1-p), \\ a_1 &= (Q_3Q_2(1-p) + Q_1Q_2(1-p) + Q_2(Q_2 + p\theta) + p\theta Q_1), \\ &= Q_2(1-p)(Q_3 + Q_1) + p\theta(Q_2 + Q_1) + Q_2^2, \\ a_2 &= Q_1Q_2^2(1-p) + Q_2^2Q_3(1-p) + p\theta Q_2(Q_1 + Q_3), \\ &= (Q_1 + Q_3)(p\theta + (1-p)Q_2)Q_2. \end{aligned}$$

Thus, all the coefficients of the polynomial (3.4.2) are positive. From the Routh-Hurwitz criterion, we can conclude that all the roots of the polynomial (3.4.2) are negative real roots. Our linearisation matrix A will thus have zero as largest eigenvalue. The statement $A1$ is verified. We now show that A_2 is satisfied.
The right eigenvector $W = [w_1, w_2, w_3, w_4, w_5]'$ and the left eigenvector $V = [v_1, v_2, v_3, v_4, v_5, v_6]$ associated to the eigenvalue 0 such that $VW = 1$ are solutions of the system:

$$\begin{cases} AW = [0,0,0,0,0,0]', \\ VA = [0,0,0,0,0,0]', \\ VW = 1. \end{cases} \tag{3.4.3}$$

Setting $w_4 = 1$ we have

$$\begin{aligned} w_1 &= -Q_1Q_2Q_3, & v_1 &= 0, \\ w_2 &= \mu Q_2Q_3, & v_2 &= \gamma(p\theta + (1-p)Q_2), \\ w_3 &= \mu\gamma pQ_3, & v_3 &= \theta Q_1, \\ w_4 &= \gamma\mu(p\theta + Q_2(1-p)), & v_4 &= Q_1Q_2, \\ w_5 &= \gamma\Big(pQ_3\delta_1 + (p\theta + Q_2(1-p))\delta_2\Big), & v_5 &= 0, \\ w_6 &= -\frac{\psi}{\omega^2\mu}\alpha_1 + \Big(\phi_1 + p\gamma(Q_3(\mu\alpha_4 + \alpha_5\delta_2))\Big). & v_6 &= 0. \end{aligned}$$

We notice that

$$\begin{cases} E_0(x_2) = 0 & \text{and} \quad w_2 > 0, \\ E_0(x_3) = 0 & \text{and} \quad w_3 > 0, \\ E_0(x_4) = 0 & \text{and} \quad w_4 > 0, \\ E_0(x_5) = 0 & \text{and} \quad w_5 > 0. \end{cases}$$

Besides, since $E_0(x_1)$ and $E_0(x_6)$ are positive, so w_1 and w_6 don't need to be positive according to Remark 1 in [7]. So statement $A2$ is verified.
The formulas of the constants a and b are

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0, \phi^*), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(E_0, \phi^*). \end{aligned}$$

After multiple derivations, we have

$$a = -2Q_1Q_2Q_3\frac{\gamma((\mu+\delta_2)(p\theta+(1-p)Q_2)+pQ_3(\mu+\delta_1))+Q_2Q_3\mu}{\gamma(Q_2(Q_3+Q_1)(p\theta+(1-p)Q_2)+p\theta Q_3)\mu S^*} < 0$$

and

$$b = \frac{\gamma(p\theta+(1-p)Q_2)^2}{Q_2(p\theta+(1-p)Q_2)(Q_3+Q_1)+p\theta Q_3} > 0.$$

Since $a < 0$ and $b > 0$, by using the fourth item of Theorem 3.4.1 we can conclude that when ϕ^* changes from negative to positive, E_0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable and a forward bifurcation appears [23].

Theorem 3.4.3. *A unique endemic equilibrium exists when $R_M > 1$ and is locally asymptotically stable.*

3.4.1 Bifurcation analysis

The study of the DFE and EE led to the proof of existence of a forward and a backward bifurcation for our model. Graphically they are respectively represented on Figure 3.2 and Figure 3.3 where R_M is chosen as bifurcation parameter. We have shown that a forward bifurcation exists for values of R_M greater than one. It means that EVD will persist as long as secondary infections will occur and reducing R_M to values less than one is enough to eradicate EVD. But the existence of a backward bifurcation makes it more difficult. In fact, the coexistence of the DFE and the EE for $R_M \epsilon [R_M^c, 1]$ shows that reducing the number of secondary infections to less than one is not enough to eradicate EVD. Others control measures like quarantine and contact tracing should be implemented together with media campaigns to reach a globally stable DFE and wipe out EVD.

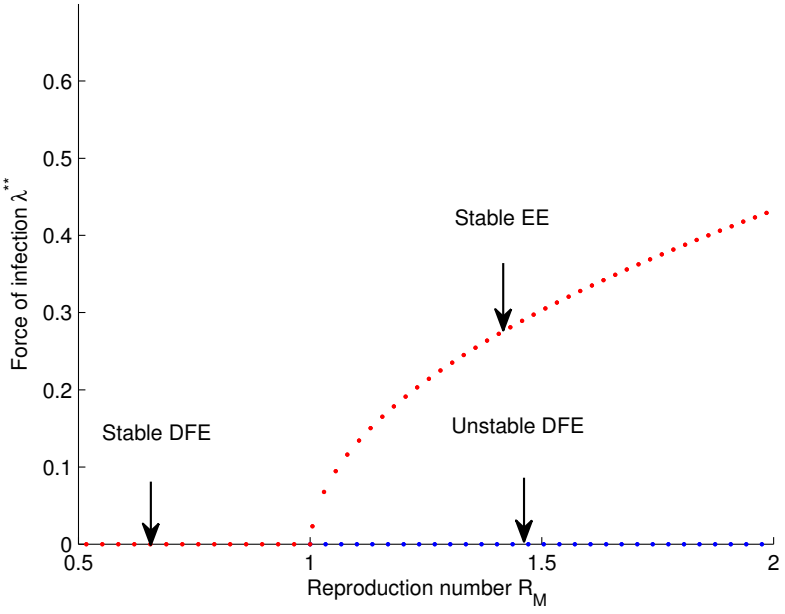


Figure 3.2: Forward bifurcation for $R_M = 1.55$

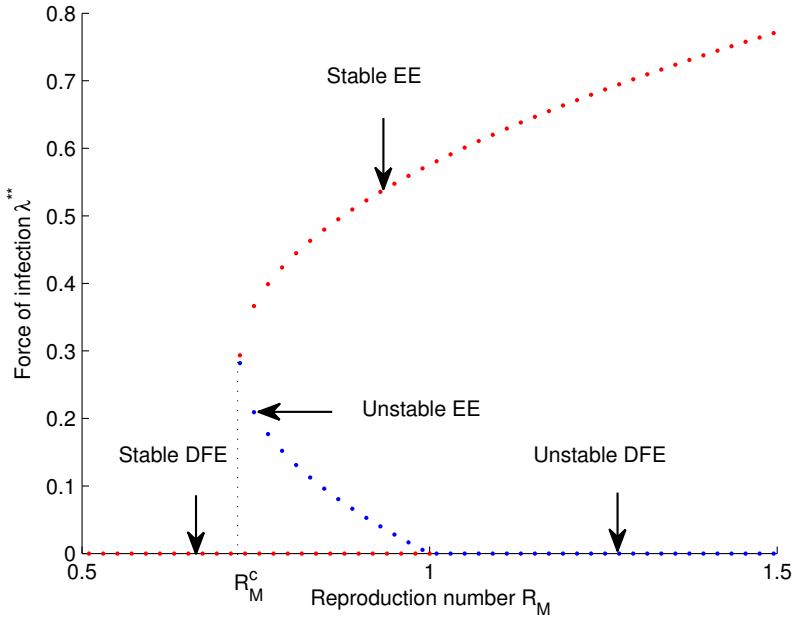


Figure 3.3: Backward bifurcation for $R_M = 0.92$

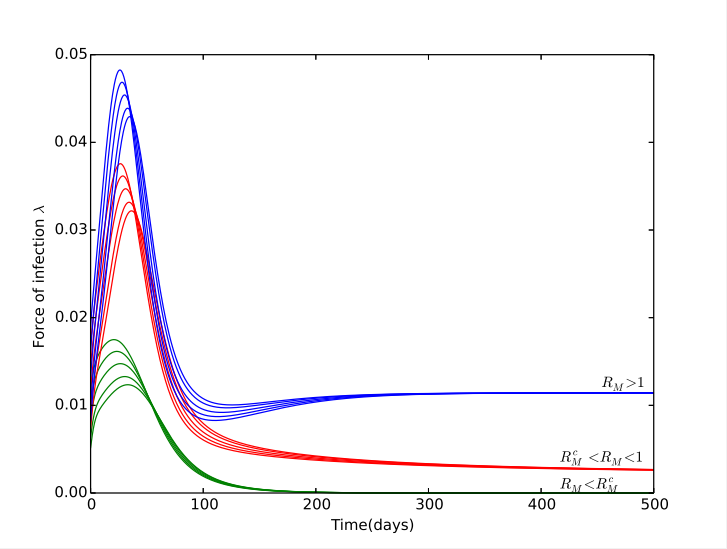


Figure 3.4: Time series variation of the force of infection for $R_M^c = 0.72$ with $\Lambda = 0.8$, $\mu = 0.0643$, $\beta\,\epsilon\,[0.05, 0.07111, 0.8]$, $c = 2.9$, $\sigma = 0.0249$, $\gamma = 0.45$, $p = 0.6559$, $\theta = 0.4640$, $\delta_1 = 0.123$, $\delta_2 = 0.603$, $\omega = 0.99$, $\alpha_1 = 0.00034$, $\alpha_2 = 0.0000649$, $\alpha_3 = 0.0000212$, $\alpha_4 = 0.0000453$, $\alpha_5 = 0.00002$.

Figure 3.4 shows time series plots for the force of infection λ for varying initial conditions. The trajectories converge to steady states depending on the initial conditions and the values of R_M. We can observe that when the DFE is globally stable ($R_M < R_M^c$), the force of infection reaches zero. When the DFE is locally stable and the EE unstable ($R_M^c < R_M < 1$), the force of infection is higher. When the EE is unstable ($R_M > 1$), the force of infection is maximal. This confirms the results obtained at the bifurcation analysis and describes the unstable nature of EVD which can easily become epidemic after a small increase of its force of infection.

3.5 Numerical simulations

In this section, we use Matlab and Python to simulate our results. We will first verify our theoretic conclusions related to stability analysis of system (3.2.1)-

(3.2.6), then we will vary our parameters values to better understand how media campaigns influence the prevalence and transmission of EVD. Then will be followed by data fitting in the model validation process.

Hypothetically, we choose a population of size 960. The initial conditions chosen wil be

$$S_0 = 900, \quad E_0 = 50, \quad I_{a0} = 0, \quad I_{s0} = 10, \quad R_0 = 0, \quad M_0 = 0.4.$$

It is important to note that the figures chosen are for illustrative purposes only, as we endeavour to verify the analytic results.

3.5.1 Parameters estimation

The parameters used in the simulations are either obtained from literature or estimated. Since the mean infectious period is set to be from 4 to 10 days, the highest recovery rate δ_2 is set to $1/4$. The recovery rate of asymptomatic individuals is assumed to be greater than the one of the symptomatic individuals since the former have a stronger resistance to the EVD. Without any reliable source for EVD related media data, we assume that everyone can send EVD related messages through media. At the beginning of the epidemic, there is neither a recovered or asymptomatic infected individual since only symptomatic persons transmit the disease. We also assume that messages are transmitted through media at time $t = 0$, at least for a preventive purposes.

Table 3.2 below gives more details about the parameters values.

Parameters	Description	Range	Source
Λ	Recruitment rate	$9\,day^{-1}$	Estimated
β	Probability for a contact to be infectious	$[0.2, 1]$	[11]
c	Number of contacts	$[1, 500]\,day^{-1}$	Estimated
γ	Rate of exposed becoming infectious	$[0.04, 0.5]\,day^{-1}$	[42]
μ	Natural death rate	$0.01012\,day^{-1}$	Estimated
p	Proportion of asymptomatic infected individuals in E	$[0.15, 0.7]$	[11]
θ	Rate of asymptomatic becoming symptomatic	$0.12\,day^{-1}$	[22]
σ	Disease related death rate	$[0.2, 0.9]\,day^{-1}$	[25]
δ_1	Recovery rate of asymptomatic	$[0.11, 0.6]\,day^{-1}$	Estimated
δ_2	Recovery rate of symptomatic	$[0.1, 0.25]\,day^{-1}$	[42]
α_1	Rate of messaging by susceptible individuals	$[0, 10^{-1}]\,day^{-1}$	Estimated
α_2	Rate of messaging by exposed individuals	$[0, 10^{-1}]\,day^{-1}$	Estimated
α_3	Rate of messaging by infected asymptomatic individuals	$[0, 10^{-1}]\,day^{-1}$	Estimated
α_4	Rate of messaging by infected symptomatic individuals	$[0, 10^{-1}]\,day^{-1}$	Estimated
α_5	Rate of messaging by recovered individuals	$[0, 10^{-1}]\,day^{-1}$	Estimated
ω	Out-dating rate of media campaigns	$[0.2, 0.5]\,day^{-1}$	[14]

Table 3.2: Model (3.2.1)-(3.2.6) parameters values

3.5.2 Simulations results and interpretation

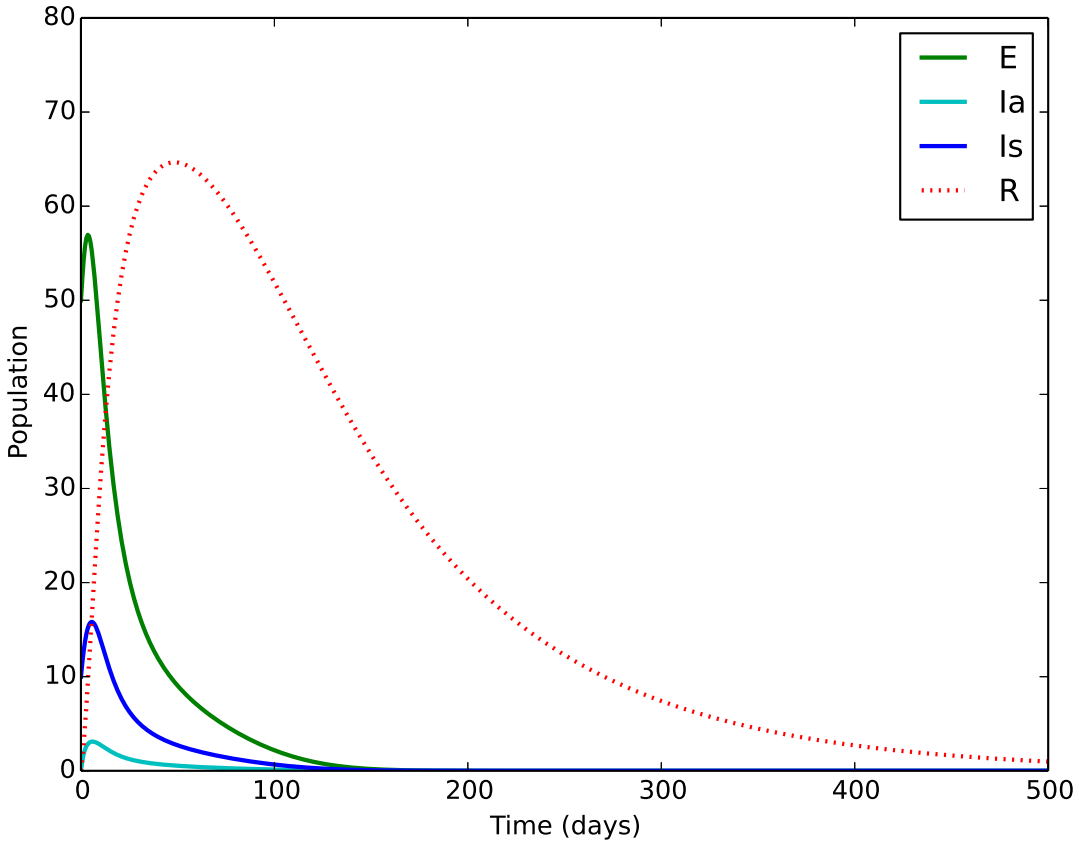


Figure 3.5: Population size at DFE for $\Lambda = 9, \mu = 0.01012, \beta = 0.19999567, c = 13, \sigma = 0.525, \gamma = 0.23511, p = 0.17, \theta = 0.12, \delta_1 = 0.513, \delta_2 = 0.13, \omega = 0.93, \alpha_1 = 2 \times 10^{-4}, \alpha_2 = 2 \times 10^{-6}, \alpha_3 = 5 \times 10^{-6}, \alpha_4 = 8 \times 10^{-6}, \alpha_5 = 9.9 \times 10^{-6}, R_M = 0.356.$

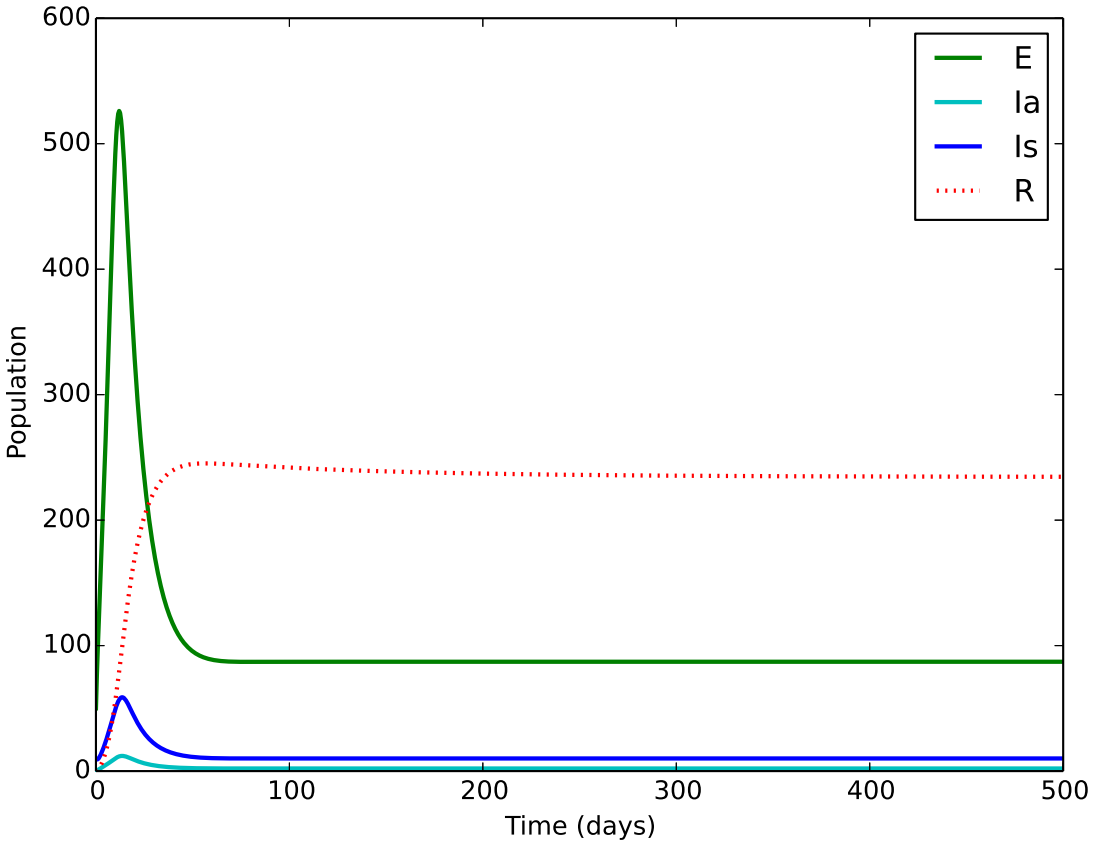


Figure 3.6: Population size at EE for $\Lambda = 9, \mu = 0.01012, \beta = 0.8, c = 15, \sigma = 0.525, \gamma = 0.09, p = 0.17, \theta = 0.12, \delta_1 = 0.513, \delta_2 = 0.13, \omega = 0.93, \alpha_1 = 2 \times 10^{-4}, \alpha_2 = 2 \times 10^{-6}, \alpha_3 = 5 \times 10^{-6}, \alpha_4 = 8 \times 10^{-6}, \alpha_5 = 9.9 \times 10^{-6}, R_M = 1.546.$

Figures 4.4a and 4.4c confirm the results on stability analysis. Then follows that when $R_M < 1$ and $R_M^c < R_M$ the epidemic dies and for $R_M > 1$, EVD becomes endemic. This is a graphical description of the fact that the DFE is locally stable for $R_M < 1$ and the EE is locally stable whenever $R_M > 1$.

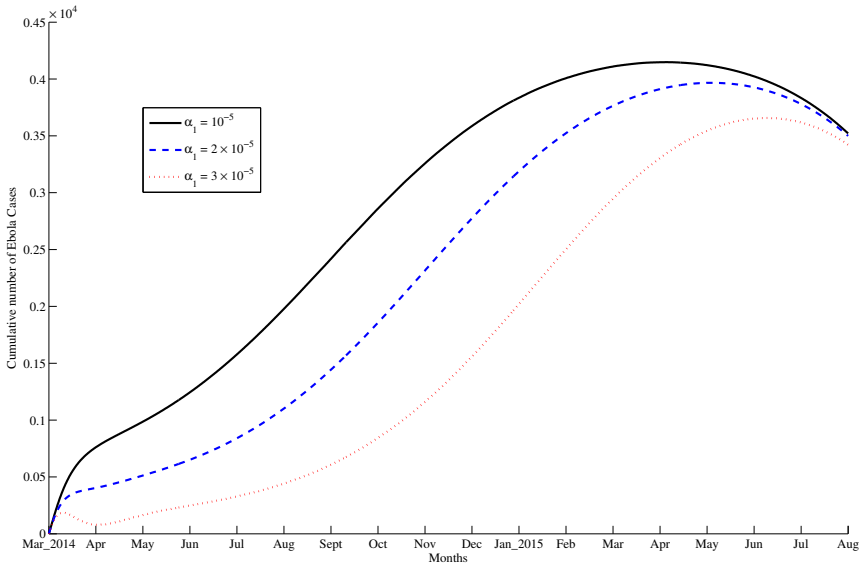


Figure 3.7: Graph of α_1 variations

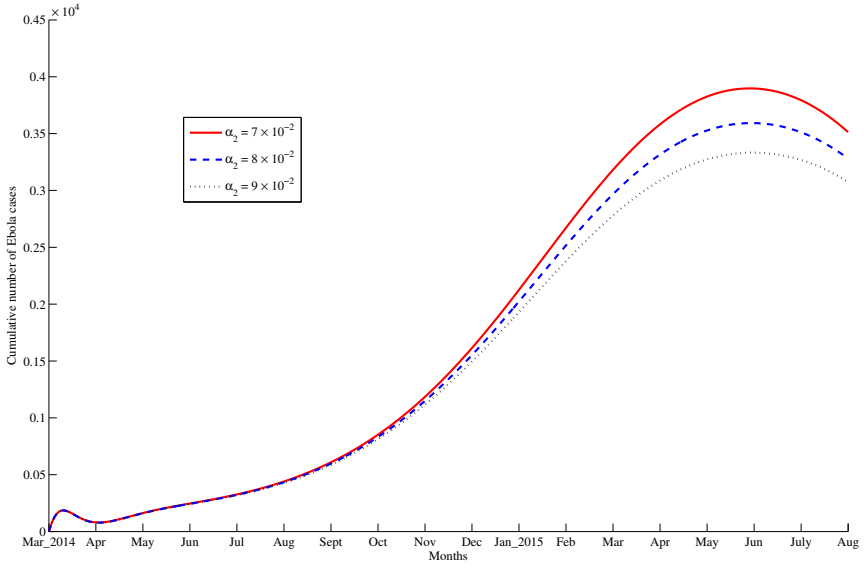


Figure 3.8: Graph of α_2 variations

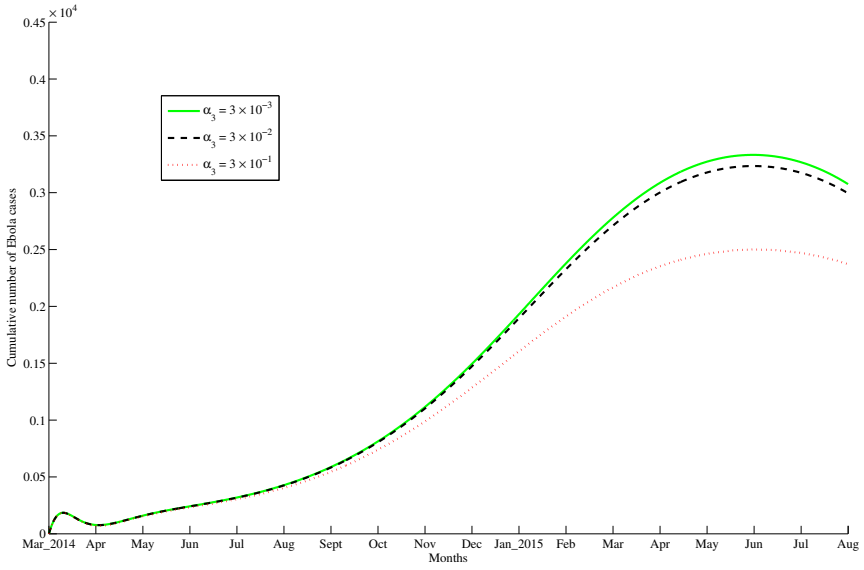


Figure 3.9: Graph of α_3 variations

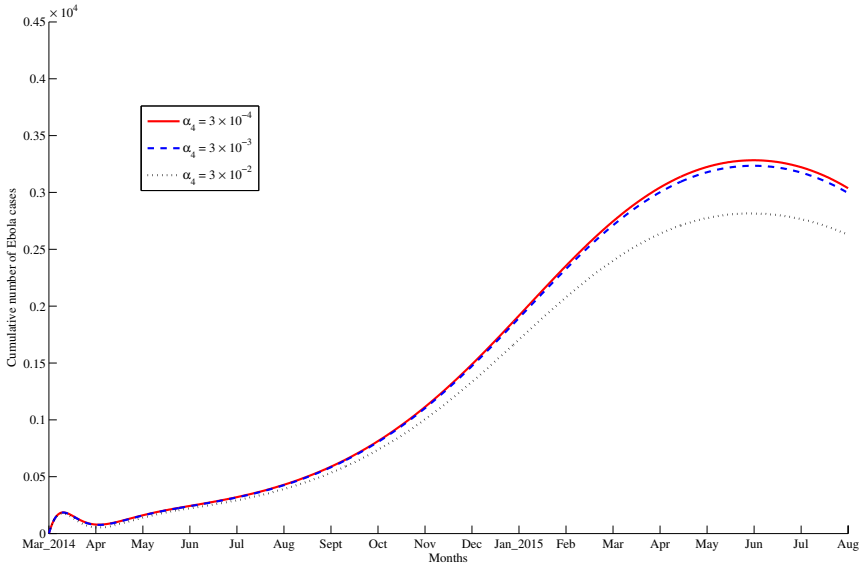


Figure 3.10: Graph of α_4 variations

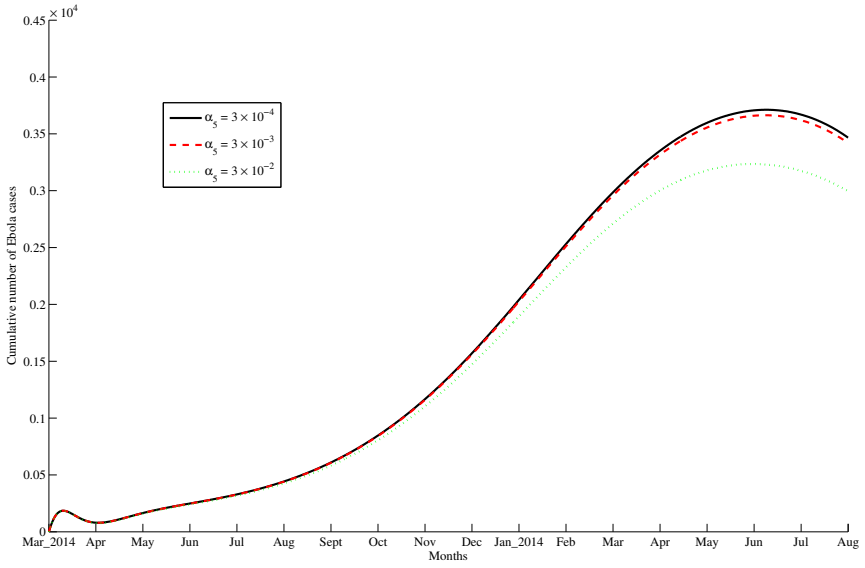


Figure 3.11: Graph of α_5 variations

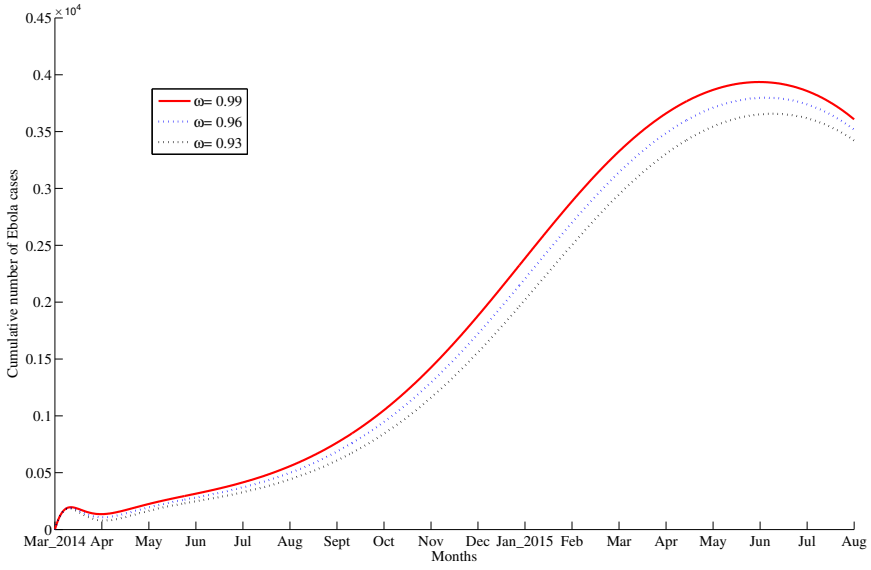


Figure 3.12: Graph of ω variations

Figures 3.7-3.11 depict the effects of increasing the sending of EVD related messages on the number of Ebola cases. We can observe a slight decrease in the number of cases when the number of messages sent are increased indicating that media campaigns alone do not induce a substantial change in the disease transmission process. That increase is more noticeable when susceptibles send more messages as in Figure 3.7. This can be due to the fact that α_1 is inversely proportional to the reproduction number and thus directly contributes to the variation of the number of new cases. It can also indicate the importance of messages sent by the uninfected class of the studied population, which is the one in charge of the infected and which informs the health care personnel. We also observe from Figure 3.12, that decreasing the out dating rate of media campaigns leads to a diminution of the number of Ebola cases. Thus, sending media campaigns with a longer duration of effectiveness is beneficial in containing the EVD outbreak. Media campaigns have to be effective and spaced in their dissemination.

3.5.3 Model validation

To validate our model, we use data obtained for Guinea during the 2014 EVD outbreak as given in [15], collected by the WHO field personnel and represented in Figure 3.14 below.

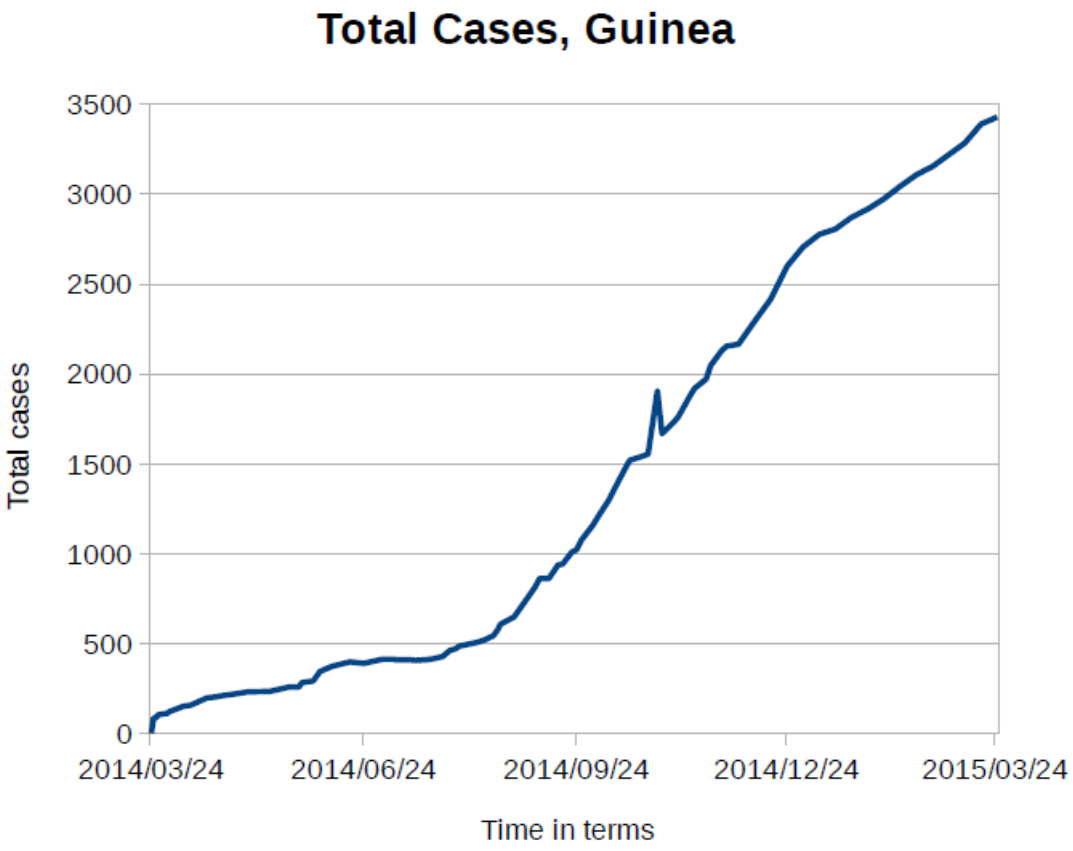


Figure 3.13: Cumulative number of suspected, probable and confirmed Ebola cases in Guinea (1 term = 3 months).

The model presented in system (3.2.1)-(3.2.6) is fitted to data in Figure 3.14. The fitting process involves the use of the least square method in which, the unknown parameter values are given a lower bound and an upper bound from which the set of parameter values that produce the best fit are obtained. Figure 3.14 and the data that produced it show a good fit for the parameter values shown in the caption. The reproduction number is correspondingly given in the caption.

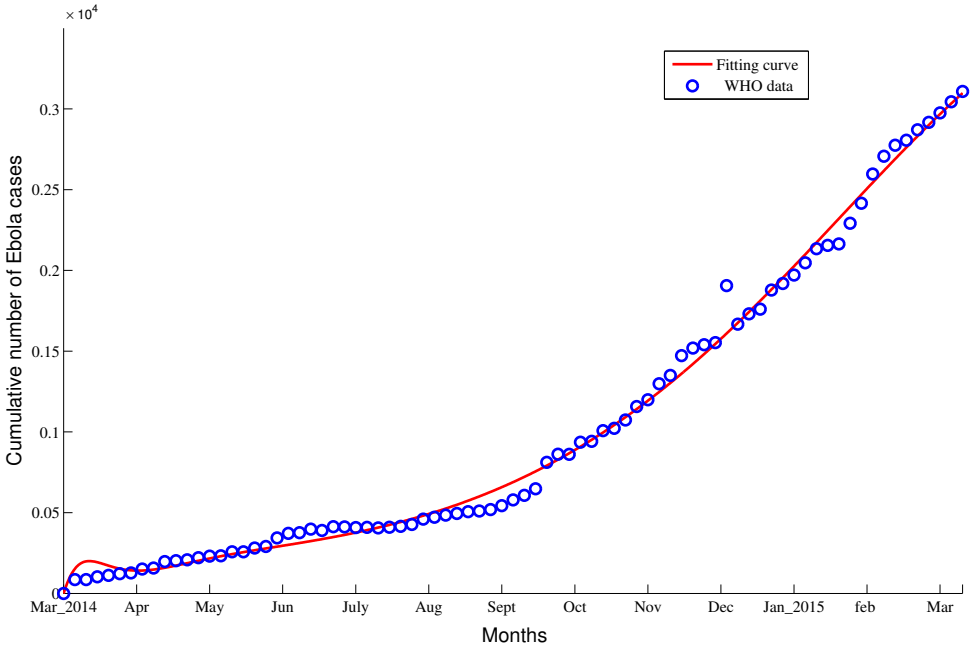


Figure 3.14: Curve fitting of the total number of Ebola cases in Guinea. The estimated parameters values are: $\Lambda = 0.8, \mu = 0.0643, \beta = 0.3, \sigma = 0.0249, \gamma = 0.1075, p = 0.6559, \theta = 0.4640, \delta_1 = 0.1231, \delta_2 = 0.0603, c = 1.57, \omega = 0.99, \alpha_1 = 34 \times 10^{-6}, \alpha_2 = 0.0643, \alpha_3 = 0.0212, \alpha_4 = 0.0453, \alpha_5 = 2 \times 10^{-10}, R_M = 2.036$.

The effective reproduction number or media reproduction number obtained from the curve fitting ($R_M = 2.036$) compares with other modelling works done so far for the case of Guinea. The effective reproduction number (R_t) estimated after a study done from July to September 2014 in [39] varies from 1.6 to 2.3, when the incubation and infection periods vary from 5 to 10 days. From a WHO Ebola response team investigations, R_t was 1.51 in Guinea as of November 2014 [49]. Just at the beginning of the epidemic in Guinea, the basic reproduction number R_0 was estimated through various studies as the implementation of controls were still awaited. The WHO team found R_0 to be 1.71 in the country. This value is higher than the effective reproduction number because in the absence of control strategies, the disease transmission is very high. Close values of R_0 in Guinea have been found by other authors. Althaus found 1.5 in [3], Shaman et al found 1.30 in [50] and Fisman et al [31] found that R_0 values lie between 1.6 and 2. The

difference within the reproduction number values obtained comes from the different calculation methods and model formulations.

From the estimated parameters, the model suggests that infected individuals do send more messages than those who are not. These results can be argued using the fact that, the health status of an individual is the major concern during an outbreak and worries increase when someone contracts EVD since there is no treatment against it. So, in order to find the best attitude to adopt against EVD, infected individuals share lots of messages through the available media. This may explain the high rate of messages exchanged by persons of the EVD infected classes. The estimated out dating rate of media campaigns is approximately equal to one. This implies that media campaigns should be frequently updated by the provision of the most recent information on prevention and treatment of the disease.

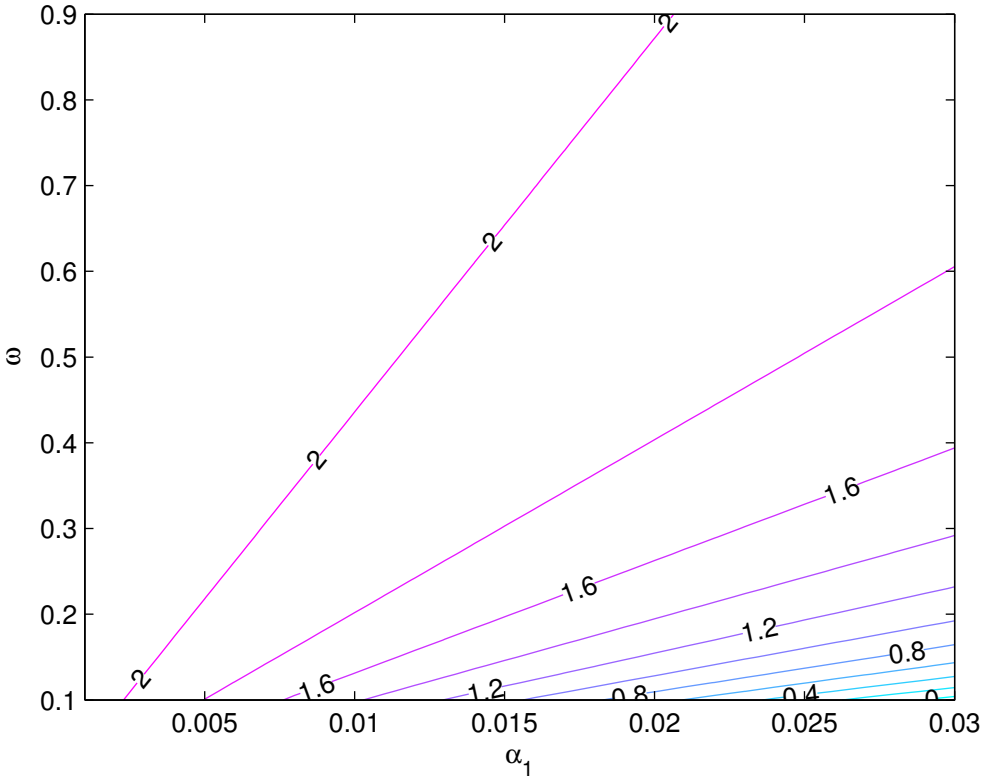


Figure 3.15: Reproduction number contour plot

The media campaigns reproduction number R_M is made of parameters which differently influence its values. The relationship between those parameters can be evaluated through contour plots. We choose two parameters, α_1 and ω, whose influence is clearly significant as shown in Figures 3.7 and 3.12. Figure 3.15 shows that α_1 largely influences R_M when compared to ω. Besides, increasing the values of α_1 decreases R_M. Thus, the exchange of EVD related messages is critical in eradicating an EVD epidemic.

3.6 Conclusion

As a conclusion to this chapter, one can retain that increasing the number of EVD related messages produces a slight decrease in the number of EVD cases and media campaigns are more effective when updated. So, the impact of media campaigns alone on the disease transmission is not significant. It is therefore necessary to implement as well, other control measures against EVD like an eventual treatment, case-finding or contact tracing in order to limit the disease spread in the population. This model describes well the dynamics of Ebola virus disease when media campaigns are used as a control measure, but it has its limitations as well. In fact, people's reaction to information on a disease is diverse and sometimes doesn't contribute to the disease eradication. Unexpected behaviours like unsafe burials or unannounced Ebola cases are still reported in the affected communities during the writing of this thesis. So, the use of an appropriated function better describing the real situation will make this model more realistic. Transmission of Ebola virus disease by asymptomatic individuals is still under investigation as of August 2015, and considering it in the transmission process can result in different disease dynamics. The cost of implementation of control measures is still an issue in the countries affected by Ebola virus disease because of their weak economic situation. Thus, in addition to media campaigns, the implementation of other control measures like educational campaigns, active case-finding and pharmaceutical interventions should be considered. A consideration of those control strategies is best done using optimal control theory which is examined in the next chapter.

Chapter 4

An optimal control model for Ebola virus disease

4.1 Introduction

The model presented in Chapter 3 does not take into consideration the most commonly used strategies in the fight against EVD. These strategies are educational campaigns, active case-finding and pharmaceutical interventions [25]. Also the previous model does not explicitly capture mortality due to the disease. In this chapter we incorporate a compartment of the deceased that is important in disease transmission.

The success of control strategies depends largely on resource mobilisation. In fact, the weak economic situations of most of the EVD affected countries was a limitation factor in the fight against the disease [37]. So, the use of effective control measures with minimal cost is observed during an epidemic. Optimal control is best described using mathematical modelling. We formulate a model for the optimal control of Ebola virus disease in this chapter.

4.2 Model formulation

Considering a large size and non constant population, we use seven independent compartments to represent individuals with different disease status. Susceptible individuals (S) are recruited into an heterogeneous population at a rate

π and will become exposed (E) after contact with Ebola virus or die naturally at a rate μ. The exposed individuals can develop symptoms at a rate γ or also die naturally at the rate μ. A proportion p of the exposed will become the infected asymptomatic individuals (I_a) while the remainder $(1-p)$ will be the infected symptomatic (I_s). Asymptomatic individuals may develop symptoms later at a rate θ and become symptomatic. They leave that class by natural death at a rate μ or recovery at a rate δ_1. Infected symptomatic compartment is decreased by hospitalisation at a rate ω, recovery at a rate δ_2, natural death at a rate μ or Ebola disease related death at rate σ_1. The hospitalized compartment (O) is diminished by recovery at a rate δ_3, death related to EVD at a rate σ_2 or natural death at the rate μ. Recovered individuals (R) can leave their class through natural death at the rate μ and dead bodies (D) are disposed at a rate ρ during funerals.

Dead bodies are highly infectious and thus contribute to the force of EVD infection together with the fluids of infectious individuals [12]. The force of infection will thus be given by

$$\lambda(t) = c\beta\frac{(I_s(t) + \eta D(t))}{N(t)} \quad \forall t \geqslant 0, \quad \text{with} \quad \eta > 1.$$

The parameter η measures the relative infectivity of dead bodies when compared to the fluids of symptomatic individuals, c is the number of contacts, β is the probability for a contact to be infectious and the total population involved in the EVD transmission is given by

$$N(t) = S(t) + E(t) + I_a(t) + I_s(t) + O(t) + R(t) + D(t).$$

The system of differential equations, describing the dynamics of EVD within the population is given by system (4.2.1) and the corresponding flow chart diagram is presented in Figure 4.1.

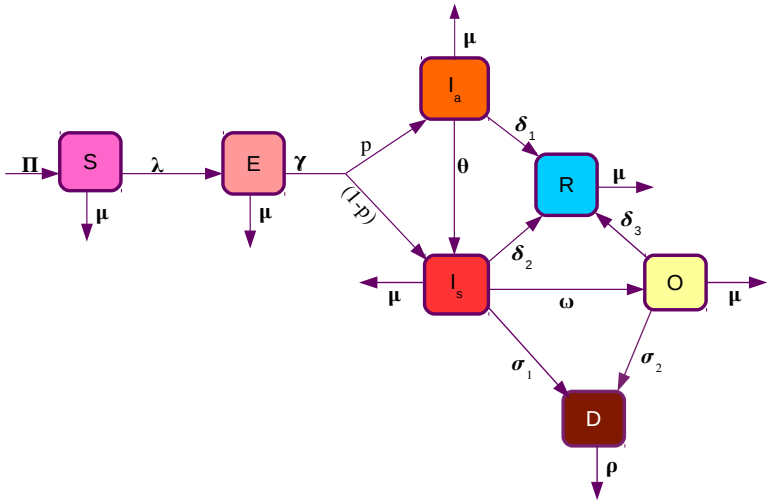


Figure 4.1: Flow diagram describing EVD dynamics.

4.2.1 Model equations

The system of ordinary differential equations describing the model is given below.

$$\begin{aligned}
\frac{dS}{dt} &= \pi - (\lambda + \mu)S, \\
\frac{dE}{dt} &= \lambda S - (\gamma + \mu)E, \\
\frac{dI_a}{dt} &= p\gamma E - (\mu + \theta + \delta_1)I_a, \\
\frac{dI_s}{dt} &= (1-p)\gamma E + \theta I_a - (\sigma_1 + \omega + \mu + \delta_2)I_s, \\
\frac{dO}{dt} &= \omega I_s - (\mu + \delta_3 + \sigma_2)O, \\
\frac{dR}{dt} &= \delta_1 I_a + \delta_2 I_s + \delta_3 O - \mu R, \\
\frac{dD}{dt} &= \sigma_1 I_s + \sigma_2 O - \rho D.
\end{aligned} \tag{4.2.1}$$

4.3 Definition and existence of an optimal control

4.3.1 Definition of an optimal control

Stopping the EVD transmission chain is still the main strategy to limit the spread of the disease. This can be done through educational campaigns which encourage behavioural changes like safe burial and self isolation [25]. This can also be done through active case-finding which consists of searching for and recording cases in the community by talking to local leaders, families or any informants. It significantly helps in limiting further contamination by Ebola virus. Once an individual is infected by Ebola virus, his chances of recovery can be increased through pharmaceutical interventions which consist of providing intravenous fluid and balancing electrolytes, maintaining oxygen status and blood pressure, treating others infections if they occur [16]. Mathematically, we define three time series controls as $u_1(t)$, $u_2(t)$ and $u_3(t)$ for $t \in [0, T]$, where T is the time duration of the interventions, to respectively represent the educational campaigns, active case-finding and pharmaceutical interventions. The implementation of educational campaigns reduces the force of EVD infection which then is modelled by the expression

$$\lambda_u(t) = c\beta(1 - u_1(t))\frac{(I_s(t) + \eta D(t))}{N(t)}, \ \eta > 1.$$

Active case finding increases the chance of hospitalization and medical care, while pharmaceutical interventions may lead to recovery. The overall objective of this chapter, which is to minimize the number of EVD cases and the cost of control strategies involved, can be mathematically translated into finding piecewise continuous controls u_1^*, u_2^*, u_3^* and associated state variables S^*, E^*, I_a^*, I_s^*, O^*, R^* and D^* that minimize the objective functional J given by

$$J(u_1, u_2, u_3) = \int_0^T \left(I_s + \frac{\alpha_1}{2}u_1^2 + \frac{\alpha_2}{2}u_2^2 + \frac{\alpha_3}{2}u_3^2 \right) \tag{4.3.1}$$

where $\alpha_i > 0$ for $i = 1, 2, 3$ are weights associated with the costs of control programs.

The optimal control problem is thus to minimize the objective functional subject

to the system of differential equations (4.3.2).

$$\begin{aligned}
\frac{dS}{dt} &= \pi - ((1-u_1)\lambda + \mu)S, \\
\frac{dE}{dt} &= (1-u_1)\lambda S - (\gamma + \mu)E, \\
\frac{dI_a}{dt} &= p\gamma E - (\mu + \theta + \delta_1)I_a, \\
\frac{dI_s}{dt} &= (1-p)\gamma E + \theta I_a - (\sigma_1 + u_2\omega + \mu + \delta_2)I_s, \\
\frac{dO}{dt} &= u_2\omega I_s - (\mu + u_3\delta_3 + \sigma_2)O, \\
\frac{dR}{dt} &= \delta_1 I_a + \delta_2 I_s + u_3\delta_3 O - \mu R, \\
\frac{dD}{dt} &= \sigma_1 I_s + \sigma_2 O - \rho D,
\end{aligned} \tag{4.3.2}$$

with positive initial conditions defined as $S(0) = S_0, E(0) = E_0, I_a(0) = I_{a0}, I_s(0) = I_{s0}, O(0) = O_0, R(0) = R_0$ and $D(0) = D_0$.

Setting (u_1^*, u_2^*, u_3^*) as the optimal controls, the minimization problem can be summarised as

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1,u_2,u_3) \in \Theta} J(u_1, u_2, u_3) \tag{4.3.3}$$

where

$$\Theta = \{(u_1, u_2, u_3) | u_i \text{ is measurable and } 0 \leq u_i(t) \leq 1 \text{ for } t \in [0, T], i = 1, 2, 3\}$$

is the set for the controls.

4.3.2 Invariance and positivity of solutions

The existing solutions of the system (4.3.2) are proven in this subsection to be invariant and positive.

Theorem 4.3.1. *The system* (4.3.2) *makes biological sense in the region*

$$\Phi = \{(S(t), E(t), I_a(t), I_s(t), O(t), R(t), D(t)) \in R^7 : N(t) \leqslant \frac{\pi}{\mu}\}$$

which is attracting and positively invariant with respect to the flow of system (4.3.2).

Proof. We assume that $\mu < \rho$ within the modelling time. This is reasonable since EVD has a higher disease induced death rate when compared to the natural mortality during the time of an outbreak. By adding all the equations of system (4.3.2) and considering $0 \leq u_i \leqslant 1$ for $i = 1, 2, 3$ we have:

$$\frac{dN}{dt} \leqslant \pi - \mu N. \tag{4.3.4}$$

Integrating (4.3.4) gives

$$0 \leqslant N(t) \leqslant \left(N(0) - \frac{\pi}{\mu}\right) \exp(-\mu t) + \frac{\pi}{\mu}, \quad \forall\ t \geqslant 0.$$

We thus have $\lim_{t\to\infty} N(t) < \frac{\pi}{\mu}$ when $N(0) \leqslant \frac{\pi}{\mu}$. However, if $N(0) \geqslant \frac{\pi}{\mu}$, $N(t)$ will decrease to $\frac{\pi}{\mu}$. So $N(t)$ is thus a bounded function of time and Φ is bounded. At limiting equilibrium,

$$\lim_{t\to\infty} N(t) = \frac{\pi}{\mu}.$$

Besides, any sum or difference of variables in Φ with positive initial values will remain in Φ or in a neighbourhood of Φ. Thus Φ is positively invariant and attracting with respect to the flow of system (4.3.2). □

Theorem 4.3.2. *The solutions of our system* (4.3.2) *are all positive.*

Proof. Considering $0 \leq u_i \leq 1$ for $i = 1, 2, 3$, from system (4.3.2) we have

$$\frac{dS}{dt} \geqslant -(\lambda(t) + \mu)S, \quad \forall\, t \geqslant 0. \tag{4.3.5}$$

Solving for (4.3.5) yields

$$S(t) = S(0) \exp\Big[-\int_0^t \lambda(\tau)\, d\tau - \mu t\Big]$$

which is positive given that $S(0)$ is also positive. From (4.3.2) we also have

$$\frac{dE}{dt} \geqslant -(\gamma + \mu)E \quad \forall\, t \geqslant 0,$$

so that

$$E(t) = E(0) \exp[-(\gamma + \mu)]t \quad \forall\, t \geq 0.$$

So $E(t)$ is positive given its positive initial conditions.
The third equation of system (4.3.2) yields

$$\frac{dI_a}{dt} \geqslant -(\mu+\theta+\delta_1)I_a \quad \forall\, t \geqslant 0$$

from which

$$I_a(t) = I_a(0)\exp[-(\mu+\theta+\delta_1)]t.$$

Thus,

$$I_a(t) \geqslant I_a(0)\exp[-(\mu+\theta+\delta_1)]t \quad \forall\, t \geq 0$$

and $I_a(t)$ is positive since $I_a(0)$ is also positive. The remaining equations yield

$$\begin{aligned}
I_s(t) &\geqslant I_s(0)\exp[-(\mu+\sigma_1+\omega+\delta_2)]t \quad \forall\, t \geq 0,\\
O(t) &\geqslant O(0)\exp[-(\mu+\sigma_2+\delta_3)]t \quad \forall\, t \geq 0,\\
R(t) &\geqslant R(0)\exp(-\mu t) \quad \forall\, t \geq 0,\\
D(t) &\geqslant D(0)\exp(-\rho t) \quad \forall\, t \geq 0.
\end{aligned}$$

So $I_a(t), I_s(t), O(t), R(t)$ and $D(t)$ are all positive for positive initial conditions. Thus all the state variables are positive. □

4.3.3 Existence of an optimal control

The existence of an optimal control is given in Theorem 4.1 formulated by Fleming and Rihel in [41] as follows:

Theorem 4.3.3. *Consider the control problem with system* (4.3.2). *There exists* $\overline{u^*} = (u_1^*, u_2^*, u_3^*) \in \Theta$ *such that:*

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1,u_2,u_3)\in\Theta} J(u_1, u_2, u_3).$$

Proof. Conditions for the optimal control to exist are the following:

(i) The set of controls and corresponding state variables, denoted Ω, is non empty.
From Theorem 9.2.1 of Lukes in [36], the solutions of system (4.3.2) exist. Thus, the set Ω is non empty.

(ii) The set Θ is convex and closed.
The set Θ is closed by definition. Given $(\theta_1, \theta_2) \in \Theta^2$ and $t \in [0,1]$ such that $\theta_1 = (u_{11}, u_{21}, u_{31})$ and $\theta_2 = (u_{12}, u_{22}, u_{32})$, the line $t\theta_1 + (1-t)\theta_2 = (tu_{11} + (1-t)u_{12}, tu_{21} + (1-t)u_{22}, tu_{31} + (1-t)u_{32})$ belongs to Θ since each of its components is in between zero and one. Thus Θ is convex.

(iii) The right hand side of the state system (4.3.2) is bounded by a linear function in the state and control variables.
System (4.3.2) is linear with respect to u_1 and u_2. Besides, its solutions are absolutely continuous [36], which implies that they are bounded and statement (iii) is then satisfied.

(iv) The integrand of the objective functional (4.3.1) is concave on Θ.
The integrand L of the objective functional is given by

$$L(I_s, u_1, u_2, u_3) = I_s + \frac{\alpha_1}{2}u_1^2 + \frac{\alpha_2}{2}u_2^2 + \frac{\alpha_3}{2}u_3^2.$$

Given $(\theta_1, \theta_2) \in \Theta^2$ and $t \in [0,1]$ such that $\theta_1 = (u_{11}, u_{21}, u_{31})$, $\theta_2 = (u_{12}, u_{22}, u_{32})$ and $t\theta_1 + (1-t)\theta_2 = (tu_{11} + (1-t)u_{12}, tu_{21} + (1-t)u_{22}, tu_{31} + (1-t)u_{32})$.

$$\begin{aligned} L(t\theta_1 + (1-t)\theta_2) &= I_s + \frac{\alpha_1}{2}(tu_{11} + (1-t)u_{12})^2 \\ &+ \frac{\alpha_2}{2}(tu_{21} + (1-t)u_{22})^2 + \frac{\alpha_3}{2}(tu_{31} + (1-t)u_{32})^2 \end{aligned}$$

and

$$\begin{aligned} tL(\theta_1) + (1-t)L(\theta_2) &= I_s + \frac{\alpha_1}{2}(tu_{11}^2 + (1-t)u_{12}^2) \\ &+ \frac{\alpha_2}{2}(tu_{21}^2 + (1-t)u_{22}^2) + \frac{\alpha_3}{2}(tu_{31}^2 + (1-t)u_{32}^2). \end{aligned}$$

Since

$$\begin{aligned} (tu_{11} + (1-t)u_{12})^2 &\geqslant (tu_{11}^2 + (1-t)u_{12}^2), \\ (tu_{21} + (1-t)u_{22})^2 &\geqslant (tu_{21}^2 + (1-t)u_{22}^2), \\ (tu_{31} + (1-t)u_{32})^2 &\geqslant (tu_{31}^2 + (1-t)u_{32}^2) \end{aligned}$$

for any $(\theta_1, \theta_2) \in \Theta^2$ and $t \in [0,1]$, $L(t\theta_1 + (1-t)\theta_2) \geq tL(\theta_1) + (1-t)L(\theta_2)$ which thus proves that L is concave.

(v) There exist constants $\eta_1, \eta_2 > 0$ and $\sigma > 1$ such that the integrand L of the objective functional satisfies

$$L(I_s, u_1, u_2, u_3) \leq \eta_1 + \eta_2(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\sigma/2}.$$

Since I_s is bounded (see [36]), there exists a constant $\eta_1 > 0$ such that $I_s \leq \eta_1$ and setting $\eta_2 = \max_{i=1,2,3} \alpha_i$ we obtain $L(I_s, u_1, u_2, u_3) \leq \eta_1 + \eta_2(|u_1|^2 + |u_2|^2 + |u_3|^2)$ with $\sigma = 2$. So, condition (v) is satisfied and the optimality system (4.3.1), (4.3.2) and (4.3.3) has a solution which is unique for T sufficiently small [34].

□

4.4 Analysis of optimal control

The optimality system (4.3.1), (4.3.2) and (4.3.3) can be converted into a problem of minimizing a pointwise Hamiltonian H with respect to u_1, u_2, u_3 thanks to the Pontryagin's Maximum Principle (PMP) in [18]. The Hamiltonian is given by

$$H = I_s + \frac{\alpha_1}{2}u_1^2 + \frac{\alpha_2}{2}u_2^2 + \frac{\alpha_3}{2}u_3^2 + \sum_{i=0}^{7} \xi_i g_i,$$

where g_i is the *ith* right hand side of system (4.3.2) and ξ_i is the *ith* adjoint. We thus have the following results.

Theorem 4.4.1. *There exist an optimal control triplet (u_1^*, u_2^*, u_3^*) and corresponding state solutions S^*, E^*, I_a^*, I_s^*, O^*, R^* and D^* that minimize $J(u_1, u_2, u_3)$ over Θ.*

Furthermore, there exist adjoint functions $\xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6, \xi_7$ *such that:*

$$\begin{aligned}
\xi_1' &= \xi_1\mu + \lambda^*(1-u_1^*)\Big(1-\frac{S^*}{N^*}\Big)(\xi_1-\xi_2),\\
\xi_2' &= \xi_2\mu + \gamma(\xi_2 - p\xi_3 + \xi_4(p-1)) - \lambda^*(1-u_1^*)(\xi_1-\xi_2)\frac{S^*}{N^*},\\
\xi_3' &= \xi_3\mu + \theta(\xi_3-\xi_4) + \delta_1(\xi_3-\xi_6) - \lambda^*(1-u_1^*)(\xi_1-\xi_2)\frac{S^*}{N^*},\\
\xi_4' &= \xi_4\mu + \sigma_1(\xi_4-\xi_7) + u_2^*\omega(\xi_4-\xi_5) + \delta_2(\xi_4-\xi_6) + (1-u_1^*)(\xi_1-\xi_2)\frac{S^*}{N^*}\kappa - 1,\\
\xi_5' &= \xi_5\mu + u_3\delta_3(\xi_5-\xi_6) + \sigma_2(\xi_5-\xi_7) - \lambda^*(1-u_1^*)(\xi_1-\xi_2)\frac{S^*}{N^*},\\
\xi_6' &= \xi_6\mu - \lambda^*(1-u_1^*)(\xi_1-\xi_2)\frac{S^*}{N^*},\\
\xi_7' &= \xi_7\mu + (1-u_1^*)(\xi_1-\xi_2)\frac{(\beta c\eta - \lambda^*)}{N^*}S^*
\end{aligned} \tag{4.4.1}$$

with transversality conditions $\xi_i(T) = 0$ *for* $i = 1,\dots,7$ *where* $N^* = S^* + E^* + I_a^* + I_s^* + O^* + R^* + D^*$ *and* ξ_i' *is the derivative of* ξ *with respect to time.*

$$\lambda^* = c\beta\frac{(I_s^*(t) + \eta D^*(t))}{N^*(t)} \quad \textit{and} \quad \kappa = \beta c - \lambda^*.$$

The following characterisation holds for $t \in [0,T]$*:*

$$\begin{aligned}
u_1^*(t) &= \min(\max(0,\bar{u}_1),1),\\
u_2^*(t) &= \min(\max(0,\bar{u}_2),1),\\
u_3^*(t) &= \min(\max(0,\bar{u}_3),1)
\end{aligned} \tag{4.4.2}$$

with

$$\begin{aligned}
\bar{u}_1(t) &= c\beta\frac{(\xi_2-\xi_1)}{\alpha_1}\frac{(I_s^*+\eta D^*)}{N^*}S^*,\\
\bar{u}_2(t) &= \omega\frac{(\xi_4-\xi_5)}{\alpha_2}I_s^*,\\
\bar{u}_3(t) &= \delta_3\frac{(\xi_5-\xi_6)}{\alpha_3}O^*.
\end{aligned} \tag{4.4.3}$$

Proof. PMP states that $\frac{d\xi_i}{dt} = -\frac{\partial H}{\partial X_i}$ evaluated at (u_1^*, u_2^*, u_3^*) with corresponding state solutions for $i = 1,\dots,7$ where X_i is the *ith* state variable respectively

chosen in $(S, E, I_a, I_s, O, R, D)$. Setting $\xi_i' = \frac{d\xi_i}{dt}$ for $i = 1, \ldots, 7$, we obtain system (4.4.1).

$$u_1^* \in \Theta \Rightarrow u_1^*(t) = \begin{cases} 0 \text{ if } u_1^* \leq 0, \\ \bar{u}_1 \text{ if } 0 < u_1^* < 1, \\ 1 \text{ if } u_1^* \geq 1. \end{cases} \tag{4.4.4}$$

$$u_2^* \in \Theta \Rightarrow u_2^*(t) = \begin{cases} 0 \text{ if } u_2^* \leq 0, \\ \bar{u}_2 \text{ if } 0 < u_2^* < 1, \\ 1 \text{ if } u_2^* \geq 1. \end{cases} \tag{4.4.5}$$

Similarly,

$$u_3^* \in \Theta \Rightarrow u_3^*(t) = \begin{cases} 0 \text{ if } u_3^* \leq 0, \\ \bar{u}_3 \text{ if } 0 < u_3^* < 1, \\ 1 \text{ if } u_3^* \geq 1. \end{cases} \tag{4.4.6}$$

Systems (4.4.4), (4.4.5) and (4.4.6) can be written as system (4.4.2).
From optimality conditions, u_i^* is solution to $\frac{\partial H}{\partial u_i} = 0$ evaluated at (u_1^*, u_2^*, u_3^*) with corresponding state solutions for $i = 1, 2, 3$.

$$H = I_s + \frac{\alpha_1}{2}u_1^2 + \frac{\alpha_2}{2}u_2^2 + \frac{\alpha_3}{2}u_3^2 + \sum_{i=0}^{7} \xi_i g_i,$$

and

$$\frac{\partial H}{\partial u_1}|_{u_1=\bar{u}_1} = \alpha_1 \bar{u}_1 + (\xi_1 - \xi_2)\frac{(I_s^* + \eta D^*)}{N^*}S^*, \tag{4.4.7}$$

$$\frac{\partial H}{\partial u_2}|_{u_2=\bar{u}_2} = \alpha_2 \bar{u}_2 + (\xi_5 - \xi_4)\omega I_s^*, \tag{4.4.8}$$

$$\frac{\partial H}{\partial u_3}|_{u_3=\bar{u}_3} = \alpha_3 \bar{u}_3 + (\xi_6 - \xi_5)\delta_3 O^*. \tag{4.4.9}$$

Solving for $\bar{u}_i$ in equations (4.4.7), (4.4.8), (4.4.9) gives system (4.4.3), for $i = 1, 2, 3$. □

4.5 Numerical simulations and results

This section is dedicated to the numerical study of the control strategies against EVD. The existence and uniqueness of an optimal control have been proven and the behaviour of the optimality system ((4.3.2), (4.4.1)), made of fourteen ordinary differential equations, is evaluated through numerical simulations done with Matlab. Some properties of the optimality system direct towards the choice of a Forward-Backward sweep method for its resolution. First, the initial values of the state variables S, E, I_a, I_s, O, R and D are given. Besides, the right hand side of system (4.3.2) doesn't contain adjoint variables. Thus, a forward Runge-Kutta 4 routine is an appropriated method used to solve system (4.3.2). Second, final time conditions for the adjoint variables are given and a backward Runge-Kutta 4 scheme is used to solve adjoint equations (4.4.1). Regarding the control values, an initial guess is first given. Then the time varying control values are found by entering the calculated values of the state and adjoint variables in the characterisation of optimal controls ((4.4.2), (4.4.3)). Convex combination is also used to update the controls values. In this case, the average of the new and old control values is taken. The convergence is acquired when the values of the variables in the new iteration and the previous iteration are insignificantly close.

The estimated parameters, among which are the weights on cost of the control programs, have been arbitrarily chosen for illustration purposes. These weight parameters determine the importance of variables in the objective functional [35]. Thus, since stopping the EVD transmission chain remains, when an outbreak has already occurred, the best opportunity to win the battle against EVD outbreaks, more importance should be given to active case-finding, a control measure during which EVD cases and their contacts are identified to limit further transmission. So, we will have $\alpha_2 > \alpha_1$ and $\alpha_2 > \alpha_3$. The parameters values used in the simulations are given in Table 4.1 below and initial conditions are estimated as:

$$S_0 = 900000,\ \ E_0 = 98000,\ \ I_{a0} = 0,\ \ I_{s0} = 2000,\ \ R_0 = 0,\ \ O_0 = 0,\ \ D_0 = 0.$$

Parameters	Description	Values	Source
π	Recruitment rate	$20000\,day^{-1}$	Estimated
β	Probability that a contact results in infection	0.008	[12]
c	Number of contacts	$20\,day^{-1}$	[12]
γ	Rate at which the exposed become infectious	$0.08\,day^{-1}$	[12]
μ	Natural death rate	$0.02\,day^{-1}$	Estimated
p	Proportion in E that become asymptomatic	0.17	[11]
θ	Rate at which those in I_a become symptomatic	$0.12\,day^{-1}$	[22]
σ_1	Disease related death rate of the infected	$0.06\,day^{-1}$	Estimated
σ_2	Disease related death rate of the hospitalized	$0.0693\,day^{-1}$	Estimated
δ_1	Recovery rate of the asymptomatic	$0.513\,day^{-1}$	Estimated
δ_2	Recovery rate of the symptomatic	$0.013\,day^{-1}$	Estimated
δ_3	Recovery rate of the hospitalized	$0.0629\,day^{-1}$	[12]
ρ	Rate of disposal of dead bodies	$0.497\,day^{-1}$	[12]
ω	Hospitalization rate	$0.3086\,day^{-1}$	[12]
η	Relative infectivity of dead bodies	1.5	Estimated

Table 4.1: Parameters values

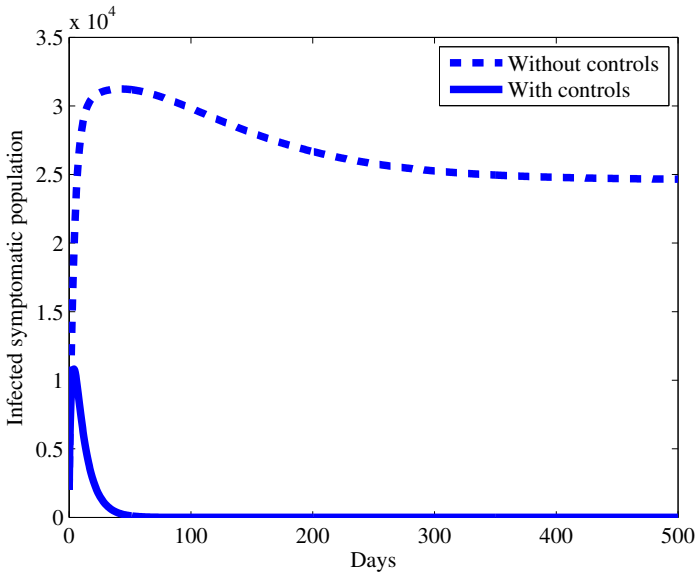
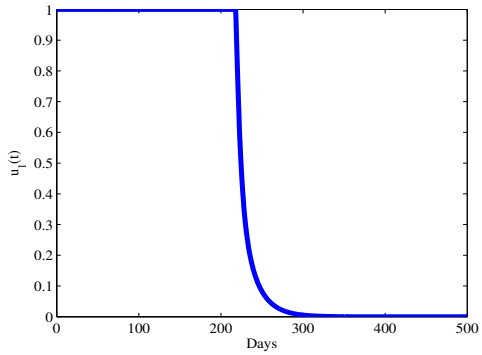
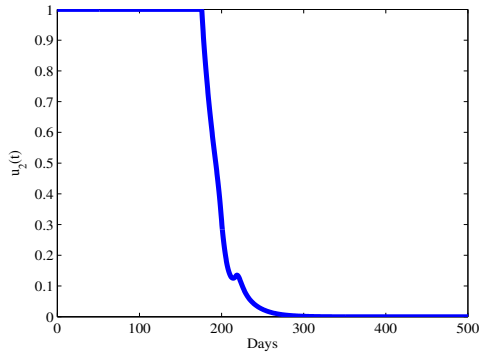


Figure 4.2: Dynamics of infected cases with and without control strategies for $\alpha_1 = 0.1, \alpha_2 = 0.3, \alpha_3 = 0.2$.

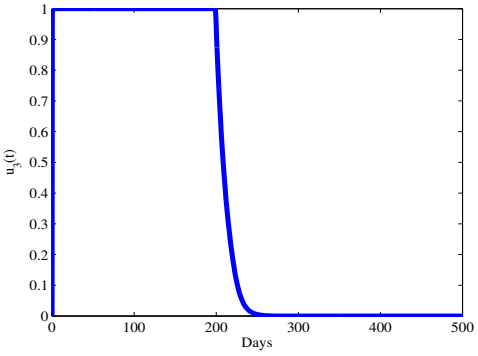
In the absence of control measures, we observe from Figure 4.2 an increase in the number of EVD infected individuals during the initial stages of the epidemic, followed by a slight decrease that lasts several days and remains at an endemic stage. In the presence of control measures, the disease out break follows a similar pattern but at a much lower outbreak numbers. An initial increase in the number of EVD cases is observed followed by a rapid decrease in the number of cases which ends at the Ebola free stage. These observations illustrate the importance of the control strategies in the reduction of the number of EVD cases.



(a) Educational campaigns



(b) Active case-finding

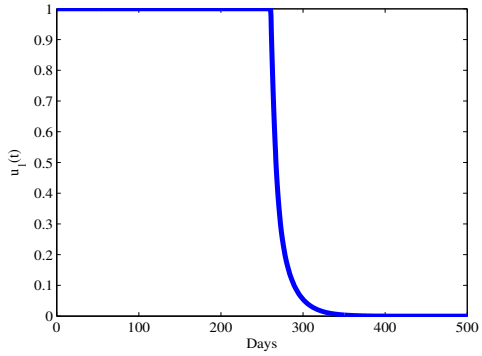


(c) Pharmaceutical interventions

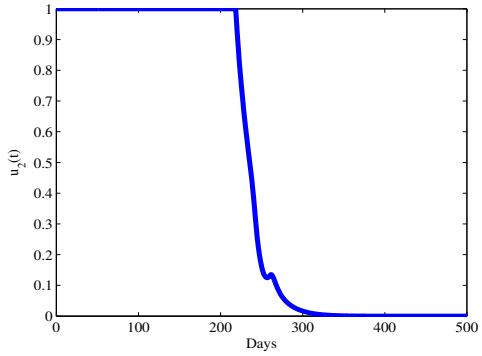
Figure 4.3: Graphical representations of control strategies for $\alpha_1 = 100, \alpha_2 = 300, \alpha_3 = 200$

Figure 4.3 shows the evolution of the control profiles over time. An interesting result is that the first two controls, u_1 and u_2, start at the upper bound while u_3 starts at the lower bound. This can be explained by the fact that in a given community, educational campaigns and case-finding are permanently implemented to raise awareness against any potential disease like EVD and to identify new cases. But, pharmaceutical interventions only start when EVD cases are hospitalized or quarantined. So, the three optimal controls should be sustained at least during 50% of the duration of an EVD outbreak (for the chosen set of our parameter values) and they should be jointly implemented in order to control the EVD epidemic. If we reduce the costs of implementing the controls, the control profiles are given in Figure 4.4, where we notice an early decrease of the

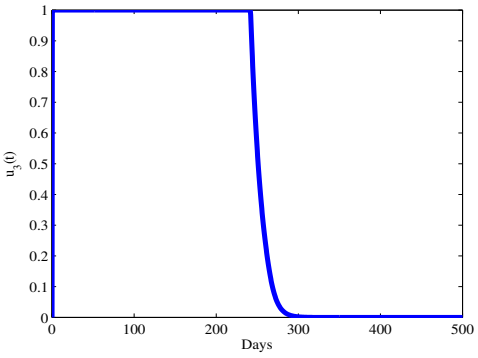
controls. This decrease in the efforts against EVD can lead to EVD persistence in an affected community.



(a) Educational campaigns



(b) Active case-finding



(c) Pharmaceutical interventions

Figure 4.4: Graphical representations of control strategies for $\alpha_1 = 0.1, \alpha_2 = 0.3, \alpha_3 = 0.2$

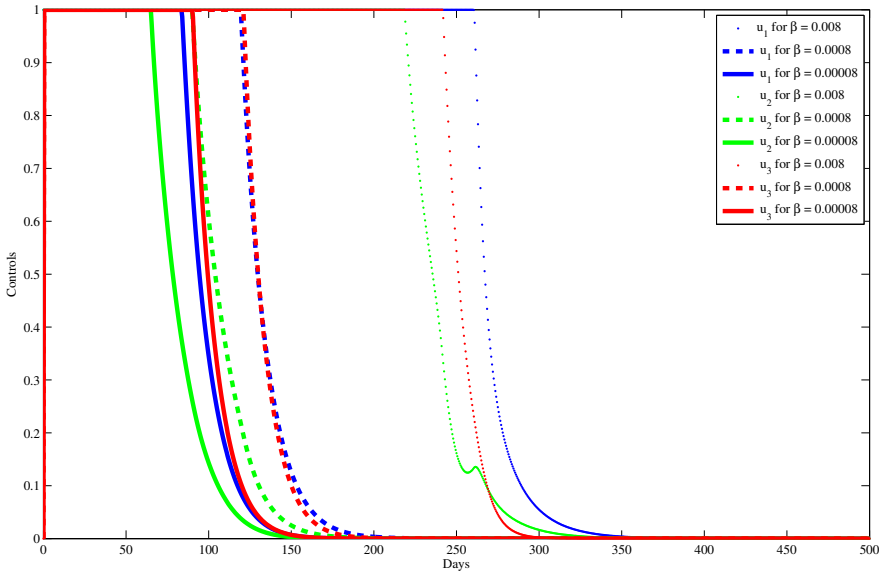


Figure 4.5: Aspects of optimal control with variations of the transmission rate

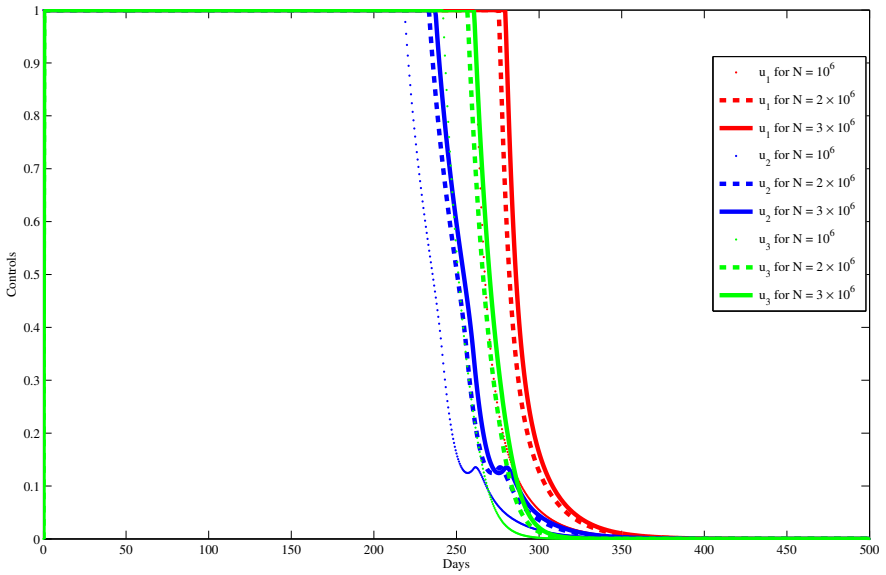


Figure 4.6: Aspects of optimal control with variations of the size of the total population

The Figures 4.5 and 4.6 depict the evolution of the control measures when the transmission rate and the total population size are varied. We notice that increasing the transmission rate or the total population size doesn't have a significant impact on the limits of the optimal controls. Figure 4.5 shows that from the beginning of the outbreak, all the three control measures stay constant for a while at the upper bound, reflecting the necessity of implementing all control strategies just as the EVD outbreak begins. Figure 4.6 also shows that increasing the size of the total population does not have an important impact on the bounds of optimal controls. These graphs thus describe the severity of EVD which should be seriously tackled just as the epidemic starts and for any given population size. To close this chapter, one can say that an optimal control of Ebola virus disease is possible through a joint implementation of the three above mentioned control measures on a long term. This model clearly gives an insight to Ebola disease evolution with controls, but it can be improved by considering for example urban and rural settings whose economic and social situations are different and thus imply different implementations of the controls. Another weakness of this model is the absence of real data (the cost of implementation of the control measures, the disposal rate of dead bodies) which would have helped in the model validation process.

This study of the impact of control measures on Ebola virus disease dynamics together with recommendations towards media, national and international stakeholders, are summarised in the general conclusion.

Chapter 5

General conclusion

The overall objective of this research project was to evaluate the impact of implemented control measures on Ebola disease evolution. First, a compartmental model comprising of individuals with different EVD infection status, who send EVD related messages through media was drawn and the role of media campaigns on EVD transmission was analysed through the model. The effects of media campaigns on people's behaviour was represented by a reduction factor which decreased the number of new EVD cases. Stability analysis was presented in terms of the model reproduction number R_M. It was shown that the disease free and the endemic equilibria are locally stable if $R_M < 1$ and $R_M > 1$ respectively. The inclusion of the asymptomatic infected class resulted in the model exhibiting a backward bifurcation, emphasizing thus the necessity of intense efforts against EVD as a result of undetected asymptomatic cases. The existence of a backward bifurcation has important implications in the design of policies and strategies to eradicate or control an epidemic. In the presence of a backward bifurcation, classical policies on disease eradication need to be changed as EVD can persist even when the threshold parameter R_M, is less than one. We chose data from Guinea, the country where this 2014 Ebola outbreak started, to validate this model. The model was fitted to the data from the CDC website [15]. The fitting process was successful and the parameter values generated through it yielded an R_M value of 2.036. The value of the reproduction number compares very well with values obtained by other researchers, see for instance [3, 39]. The model evaluated the impact of media campaigns on the reduction of the number of Ebola cases through numerical simulations and we have observed

a decrease in the prevalence of the disease when media campaigns were used as control strategy. This first model is not without shortcomings. The reaction to media campaigns by individuals doesn't always lead to a reduction in the number of future contaminations. So, a function representing the influence of media campaigns on individuals' behaviour and which takes into account the different cultural settings would be an innovative and informative addition to this model. Aspects of quarantine, contact tracing and case identification initiatives are possible additions that can make this model more reliable.

Second, an optimal control of Ebola disease was described by a seven compartments deterministic model, obtained by extending the previous one to hospitalized and dead individuals. They were considered together with educational campaigns, active case-finding and pharmaceutical interventions as control strategies implemented to limit the number of individuals entering the exposed and dead classes. The existence of an optimal control set was proven and its analysis was done using Pontryagin's Maximum Principle. The simulations results showed that optimal control of Ebola virus disease is doable through educational campaigns, active case-finding and pharmaceutical interventions. They showed as well that a long term support for the joint implementation of those control strategies was needed for better results. The variation of the total population size indicated that independent of the size of the population, interventions against any Ebola disease outbreak should begin at the onset of the epidemic for rapid and effective control. This second model of Ebola disease is not without limits as well. The weights on cost considered here are for illustrative purposes. More realistic results will be obtained if real data on the cost of the implementation of control strategies are used. One of the challenges here is the fact that the 2014 Ebola outbreak is still ongoing during the writing of the thesis and only partial data on the cost of the disease eradication are available. Once the epidemic will be declared over, statistics on its burden will be available and a better cost-effectiveness of the disease will be obtained. Another shortcoming of this model is the estimated value of the rate of disposal of dead bodies. Unsafe burials of Ebola related dead individuals are still denounced in countries like Guinea, and that makes it difficult to find the exact number of Ebola deaths and the rate at which they are buried. Despite the shortcomings, these models still

provide some useful insights into the control of EVD through the implementation of the discussed control measures.

The study done in this thesis recommends a better collaboration between health authorities and media for an early announcement of any epidemic, frequent updates of informations sent by media related to Ebola disease, a joint implementation of all the control strategies studied, the provision of sufficient financial resources for a sustained implementation of the control measures by national and international organisations.

These models can be extended by considering rural and urban settings separately, where the implementation of controls is not done at the same scale. Cultural beliefs are deeply anchored in people's behaviours in rural settings and changing of habits as prescribed by health care givers is therefore more difficult. So, the choice of the control strategies, which take into account the realities of the affected countries remains the best option in the fight against Ebola virus disease. Since the transmission of Ebola disease by asymptomatic infected individuals is still being investigated at the time of writing this thesis, considering it in a future Ebola disease dynamics model can be an innovation as well.

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